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CLINICAL AND EXPERIMENTAL STUDIES ON C-REACTIVE PROTEIN (ACUTE PHASE PROTEIN)

By

PER HEDLUND

STOCKHOLM 1961

CONTENTS

Roman numerals refer to previous publications.

This survey is based on the following publications

I HEDLUND, P The Production of the Acute Phase Protein after Nonspecific Stimulation. Acta Med. Scandinav 118, 329—344 1944

II HEDLUND, P The Appearance of Acute Phase Protein in Various Diseases. Acta Med. Scandinav suppl. 196 579—601 1947

III HEDLUND, P., FRISK, A. R. and BUCHT H. The Appearance of Acute Phase Protein after Induced Fever in Man. Acta Med. Scandinav 131 417—421 1948.

IV HEDLUND, P., FRISK, A. R. and BUCHT H. The Effect of Salicylic Acid Medication on the Formation of Acute Phase Protein in the Blood. Scandinav J Clin. Lab. Investigation 8, 207—212, 1956

V HEDLUND P and BRATTSTEN I Electrophoretic Analysis of Human Acute Phase Protein. Scandinav J Clin. Lab. Investigation 7 99—100 1955

VI HEDLUND, P and BRATTSTEN, I. Isolation of Acute Phase Protein by Means of Continuous Zone Electrophoresis. Scandinav J Clin. Lab. Investigation 8, 213—222, 1956.

VII HEDLUND P A Comparison between the Löfström Capsular Swelling Reaction and the CRPA Method (C-Reactive Protein Antiserum) for Determination of Acute Phase Protein in Human Serum. Scandinav J Clin. Lab. Investigation 9 218—222, 1957

VIII HEDLUND, P Absorption Experiments with Acute Phase Protein in Human Serum. Acta Path. Microbiol. Scand. 45 267—274 1958.

In the following these publications are referred to under their Roman numerals. The contents of Chapters 3 4 and parts of 5 have not been published before. The greater part of Chapter 7 was presented at the European Congress of Cardiology in London in 1952 and a part of Chapter 8 at an annual meeting of the Swedish Medical Society in 1955

INTRODUCTION

During the course of this work carried out both in clinic and laboratory since 1943 many problems of theoretical and practical interest have arisen. The primary goal of the clinical work has been to find out under which pathological conditions the C-reactive protein (CRP) appears and of what help its demonstration may be for the diagnosis. Special attention has been devoted to its occurrence in rheumatic diseases, myocardial infarction and diseases of the liver. The experimental part of the studies deals with the sensitivity of the two methods for CRP determination most commonly used in routine clinic work, and various ways of inducing acute phase protein in animals. Experiments have also been performed on humans in order to study the appearance of CRP after non-specific stimulation and salicylic acid medication. Finally the properties of CRP were studied in electrophoretic and absorption experiments.

CHAPTER 1

Historical Review

C-reactive protein or acute phase protein" as it is also called appears in human blood under several different pathological conditions. It is not found in healthy individuals. The substance was detected in 1930 by Tillett & Francis (138) who found that a precipitate was formed when pneumococcal C-polysaccharide was added to the sera of patients with acute pneumonia but not when added to sera obtained after the crisis. Thus it has been clear from the very beginning that the C-reactive substance is not an antibody. The same authors also found that the active substance occurs not only in pneumococcal diseases but also in a number of other infectious diseases such as acute rheumatic fever bacterial endocarditis and staphylococcal osteomyelitis.

In 1939 Löfström (79 80, 81) described a substance which, under certain conditions, occurred in blood serum and caused non-specific swelling of the capsules of pneumococci of types 27 and 28 and at times of other types too. With his non-specific capsular swelling reaction (CSR) Löfström demonstrated the active substance in the blood of patients with acute pneumonia and in cases of respiratory tract infections known to have a tendency to cause bacterial complication. Löfström designated this substance "non-specific capsular swelling substance" In 1944 he proved that the substance was identical with C-reactive protein (CRP) (82)

Biochemical properties. The proteinic nature of the C-reactive substance was revealed by Abernathy & Avery (4) in 1941 They found that the substance in diluted serum was inactivated after exposure to temperatures above 65 C. They also found, by salting out the active serum with ammonium or sodium sulphate, that the C-precipitable substance was carried down with the albumin fraction. Abernathy and Avery's results indicated that the reactive substance in serum is protein in nature" They also made the important observation that calcium ions are necessary for the reaction. The occurrence of CRP only *during the acute stage of an infection*, its lack of specificity and the necessary presence of calcium ions for precipitation are all characteristics which differentiate this reaction from an antigen-antibody reaction.

In 1941 McLeod and Avery (85) succeeded in isolating CRP from the fraction of serum albumin precipitated by ammonium or sodium sulphate between 50 and 75 saturation. They also showed that the solubility of the reactive protein was influenced by calcium ions as well as by lipids. After removal of the alcohol-ether soluble lipids

from acute phase serum the CRP lost its calcium sensitivity and remained soluble on tap water dialysis.

Several electrophoretic analyses of acute phase serum have been made but results have not been conclusive. Perlman, Bullowa and Goodkind in 1943 (107) established that CRP migrated with the alpha-globulin fraction. Concurrently Löfström (81) using a special technique for the separation of different serum fractions, showed that the non-specific capsular swelling substance belonged to the globulin fraction and moved faster than the gamma-globulins. In 1954 Wood, McCarty and Slater (149) in a free electrophoretic study found that crystalline CRP migrated as a beta-globulin. When zone electrophoresis of an acute phase serum in a starch medium was performed they found the active substance to migrate with the fast component of the gamma-globulins. By using continuous zone electrophoresis Hedlund & Brattsten in 1955 (55, 57) showed that the acute phase protein in human serum migrated with the gamma globulins. The following year Philipson & Tveteräs (109) found the active substance between the beta and gamma globulins.

The antigenic properties of the C-reactive protein were also studied by McLeod and Avery in 1941 (86). They found that purified human CRP injected into rabbits produced antibodies. The antiserum obtained reacted specifically with the purified C-protein as well as with acute phase serum from humans and monkeys having acute bacterial infections. The immunological specificity of the CRP was demonstrated by precipitin and complement fixation tests. The sensitivity of the test for CRP was higher with antiserum than with C-polysaccharide. In 1947 McCarty (87) prepared the active substance in crystalline form from human serous fluids. Wood McCarty and Slater (149) modified the technique and obtained a high yield of crystalline protein. This method has made the commercial production of antisera for clinical tests possible.

Methods for detection. CRP in human serum can be demonstrated by three main methods

1) The original method of Tillett and Francis (138) where pneumococcal C-polysaccharide is the reagent. Calcium ions are necessary for the reaction which results in a precipitate of C-protein-carbohydrate.

2) The non-specific capsular swelling *reaction* (CSR) *of pneumococci type* 27 or 28 according to Löfström (80, 81). This reaction is also dependent on the presence of calcium ions.

3) McLeod and Avery's method (86). A specific rabbit antiserum gives a precipitate when mixed with acute phase serum. Being an antigen-antibody reaction this precipitation is independent of the presence of calcium ions. The method has been adapted as a capillary precipitin test for routine clinical studies (8).

The original method of Tillett & Francis incorporating pneumococcal C-polysaccharide is less sensitive than the other methods. In 1957 a study on the sensitivity of the Löfström capsular swelling reaction and the C-reactive protein antiserum method was performed by Hedlund (58). The two methods seemed to be equally sensitive. Attempts have been mad to increase the sensitivity of the CRP test and to make it simpler to perform. Such techniques as

latex particle-agglutination (latex fixation test) (130) hemagglutination (42) complement fixation tests (98, 112) and precipitin analysis by gel diffusion (74 76 112) have been described in this connection.

Occurrence in various diseases In 1933 Ash (10) examined sera from patients with different infectious and non-infectious diseases for the presence of C-reactive protein. She was able to demonstrate the substance in sera during the acute stage of infections due to gram-negative as well as gram-positive microorganisms, during the acute stage of rheumatic fever and sometimes also during the acute stage of tuberculosis. In 1934 Francis and Abernathy (40) described a characteristic skin reaction after an intracutaneous injection of C-polysaccharide given to patients in the acute stage of pneumonia. This skin reaction was correlated to the CRP reaction of the serum. Their results were confirmed by Finland and Dowling in 1935 (37) and by themselves in 1937 (2)

In his brief review in 1943 of the non-specific capsular swelling of pneumococci Löfström (81) described the appearance of the substance in various diseases. Almost every case in the acute stage of bacterial disease such as pneumonia, sepsis and paratyphoid fever showed active substance. It occurred less regularly in such diseases as scarlet fever and pulmonary tuberculosis. With a few exceptions, cases of virus infection lacked non-specific capsular swelling substance in the blood An interesting observation was made by Löfström as early as 1942 (80) when he found the substance in cases of myocardial infarction. The finding is of particular interest because in this ailment there is merely a resorption of disintegrated tissue and no infection. Löfström examined only a few cases of malignancies and found the substance in some of them.

A general clinical evaluation by Hedlund in 1947 (52) reported the appearance of CRP in various diseases. In this review it was shown how the active substance occurred in cases of appendicitis, diseases of the biliary ducts, acute hepatitis, disorders of the urinary tract, myocardial infarction, pulmonary embolism, neoplasms and various other ailments. The difference in the behaviour of the C-reactive substance in cases of rheumatoid arthritis and rheumatic fever was also pointed out.

Experimental induction in humans and animals The same year that Löfström demonstrated the non-specific capsular swelling substance in non-bacterial diseases, Carlens (28) demonstrated it 24 hours after sterile operations on the knee where any form of active infection could be ruled out. Carlens also induced the substance experimentally in humans by injections of sulphur suspended in oil (Allergol) Similar experiments were made by Löfström (81) In 1944 Hedlund (51) tested several agents thought to be effective in non-specific stimulation to investigate their ability to produce Löfström's substance. In man, type 27 reactive substance was produced after injections of manganese salt, sulphur and typhoid vaccine.

Soon after its discovery experiments were made to induce the C-reactive substance in healthy animals. In 1937 during the course of experimental infection of monkeys, Abernathy showed that these animals reacted in the same way as man to spontaneous disease (3) A substance having similar properties to the active substance in humans

was demonstrated in rabbits by Löfström (81) but this rabbit substance reacted best with type 16 pneumococci (later shown to be identical with type 11 A) (83) In 1951 Anderson & McCarty (9) confirmed that a protein with properties very alike to human CRP could be induced in the serum of rabbits.

After sterile operations on the knee Carlens (?8) in 1941 found that the CSR was positive after 15—24 hours. Experiments on humans performed in 1947 by Hedlund, Frisk & Bucht (54) showed that CRP appeared in the blood 15—21 hours after the onset of stimulation. In 1956 the same authors demonstrated it as early as 12—14 hours after the administration of vaccine to humans (56) Anderson and McCarty confirmed these results in that they showed CRP in the blood by the eighteenth hour after stimulation (9) Using another agent on human subjects Stollerman, Glick and Anderson in 1954 (135) detected CRP 6—12 hours after stimulation. The appearance time is the same in rabbits and man

Treatment of rheumatic fever with adequate doses of salicylate is followed within a few days by the disappearance of CRP (Hedlund 1947 (52) Rothbard et al. 1948 (119) Anderson, McCarty 1950 (8) Its appearance or disappearance during the course of rheumatic disease has proved to be a good guide when following the effect of treatment. Adequate doses of cortisone suppress the rheumatic inflammatory activity and the CRP disappears (McEwen et al. (90) This usually occurs within the first week of treatment (Stollerman et al. (134)

The non-specific capsular swelling reaction detected by Löfström was simple enough to perform and could thus be used as an aid for diagnosis. His method is advantageous in that it can be used both on human and animal material. Löfström saw the possibility of using the capsular swelling reaction as a diagnostic method in the clinic and gave examples of diseases in which it might be of practical value and interest to know the acute phase protein titer A charting of different pathological conditions in which CRP appears and of its behaviour in human disease was presented by Hedlund in 1947 (52) The results obtained in this review were confirmed some years later when it was possible to use specific rabbit antiserum according to McLeod and Avery (86) in the capillary precipitin test described in 1950 by Anderson and McCarty (8) Nowadays the determination of the CRP titer has become routine in clinics all over the world.

EXPERIMENTAL STUDIES

CHAPTER 2

The Sensitivity of the Capsular Swelling Reaction (VII)

In order to demonstrate CRP in human serum in routine clinical work the Löfström capsular swelling reaction (CSR) and the C-reactive protein antiserum (CRPA) methods are extensively used. In all clinical studies presented here the human sera have been examined with the CSR method. When CRPA became commercially available and began to be used in the clinic it was questioned whether the two methods were equally sensitive. An investigation as to their relative sensitivity was therefore performed (VII).

Most blood serum samples were examined the day after removal from the patient and then kept frozen at −20° C. As already observed by Löfström (81) uncontaminated clear sera kept frozen at −20° C have shown an unchanged CSR titer for years. This fact has made it possible to store positive sera with a known titer at −20° C and to use them as standards for checking the pneumococcal suspensions which were produced and used in all CRP determination work. Furthermore the CRP positive samples won at electrophoretic fractionation could be stored at −20° C for months without losing their activity (VI p. 215).

The sera used for examination were obtained from patients with different diseases, many of them from cases of infectious hepatitis. As the production of CRP in this disease is often very low, serum from patients with hepatitis is particularly suitable for demonstrating the sensitivity of the methods.

In this study special efforts have been made to avoid methodical errors. The CSR method involves two sources of error: the serum might contain specific antibodies to the pneumococci used for the examination, and double refraction in the microscope may give a false indication of a positive reaction. Both these difficulties are easily overcome. When a reaction mixture free of calcium ions is used the CRP causes no capsular swelling of the pneumococci whereas the specific antibodies react independently of calcium ions. Double refraction is avoided by exact centering of the light in the microscope.

When the columns of CRPA and test serum are drawn up into the capillary tube it is necessary to check that contact between the two sera has been established. A bubble of air between excludes any possibility of reaction. When using the

Table I. The appearance of acute phase protein in mice, hens and guinea pig stimulated with typhoid vaccine

Animals		CSR titer with pneumococcus type					
		11 A		23 B		27	
		With Ca^{++}	Without Ca^{++}	With Ca^{++}	Without Ca^{++}	With Ca^{++}	Without Ca^{++}
Mouse no.	1	1	0	1	0	1	0
	2	0		1	0	0	
	3	1	0	1	0	1	0
	4	0		4	0	1	0
	5	0		1	0	0	
	6	1	0	1	0	0	
	7	0		1	0	0	
	8	0		1	0	0	
	9	1	0	1	0	0	
	10	0		1	0	0	
Hen no.	1	2	0	1	0	1	0
	2	2	0	0		1	0
	3	2	2	1	0	1	0
	4	1	0	0		1	0
	5	2	0	0		1	0
	6	4	2	0		1	0
Guinea pig no.	1	0		1	0	1	0
	2	0		1	0	1	0
	3	1	0	1	0	0	
	4	0		0		1	0
	5	0		0		0	
	6	0		0		0	

and baby rabbits were bled by cardiac puncture (0.8 mm needle for the hens and guinea pigs, and 0.5 mm needle for the mice and baby rabbits). All blood samples were kept at room temperature overnight, centrifuged, and the sera examined immediately and kept frozen at —20 C for a control examination.

Typhoid vaccine. Containing 10 bacteria per ml and preserved in 0.5 % carbolic acid.

Sulphur preparation. Manufactured by the Swedish firm Leo under the name Neosulforin and containing sulphur sublimatum steril 0.005 g, guajacol 0.005 g, camphora 0.03 g, benzocain 0.04 g, Ol. amygdalae ad 1 ml.

CSR method. Described in Paper VII. Suspensions of pneumococci types 11 A, 23 B and 27 were the test agents used. The serum samples were also tested without calcium ions in the reaction mixture as described in the same paper.

Experimental

Two sets of experiments were performed on hens, guinea pigs and mice. In the first, 5 hens, 5 guinea pigs and 5 mice were used. The experiment was repeated three weeks later on the same number of new animals. Each of the hens was given 0.5 ml typhoid vaccine intramuscularly, each of the guinea pigs

Table 2 CSR in baby rabbits of varying age stimulated with injections of typhoid vaccine and sulphur

Number of rabbits	Age	Intramuscular injection of	Number of rabbits giving positive CSR			
			before injection		20—24 hours after injection	
			type 11 A	type 23 B	type 11 A	type 23 B
6	2 hours	Typhoid vaccine 0.1 ml				0
4	2—4 hours	Typhoid vaccine 0.2 ml	0	0	1	1
8	2—6 hours	Neosulfosin 0.25 ml			0	2
4	24 hours	Typhoid vaccine 0.3 ml			0	4
6	3 days	Typhoid vaccine 0.3 ml			0	6
3	1 month	Typhoid vaccine 0.4 ml	0	0	2	3
2	1 month	Neosulfosin 0.25 ml	0	0	1	1

0.5 ml subcutaneously and each of the mice 0.2 ml subcutaneously. In the first set of experiments the animals were bled 20 hours after injection and in the second set 28 hours after injection.

Pregnant female rabbits were placed under observation in order to take the young as soon as possible after birth. The youngest litter consisted of six individuals 2 hours old. One litter of four was 2—4 hours old and one of eight 2—6 hours old. Four further litters were 1 day 3 days, 7 days and one month old as seen in Table 3. No CSR was made before injecting the very young rabbits (except for one litter 2—4 hours old) as the cardiac puncture often led to their death. After the animals had reached the age of one month there was no danger of killing them by this procedure. All animals were injected intramuscularly in the thigh. The dose of typhoid vaccine varied from 0.1 to 0.4 ml and the Neosulfosin was 0.25 ml as seen in Table 2. As it was difficult to get sufficient amounts of blood by cardiac puncture from the 2-hour old animals their serum was only examined with pneumococci type 23 B.

Results

The results of the experiments are to be seen in Table 1. When calcium ions were present in the reaction mixture all mice sera reacted with type 23 B, four of the sera with type 11 A and three with type 27; all hen sera reacted with type 11 A and 27 and two of the sera with 23 B; one of the guinea pig sera reacted with type 11 A, three with type 23 B and three with type 27. On the exclusion of calcium ions, all the positive sera were negative except sera from two hens (nos 3 and 6) which reacted with type 11 A. Hen 3 serum had an unchanged titer 2 and the titer for hen 6 serum decreased from 4 to 2.

Table 2 presents results of the experiments on baby rabbits. No reactive substance could be shown in the animals about 2 hours old. Only three very young animals (2—6 hours old) gave positive reactions, one after a typhoid injection and two after sulphur injections. When more than 24 hours old, all reacted positively. After stimulation, titers for all positive animals ranged between 1 and 4. The five one-month old rabbits were also tested after 70 hours. All had a

negative CSR with both types of pneumococci. None of the positive sera in this experiment gave a positive CSR in the absence of calcium ions.

Discussion

Löfström showed that horse and guinea pig sera contained normal antibodies (81). A characteristic of these normal antibodies is that they are independent of calcium ions. None of the guinea pigs and mice in the experiments included in this work showed antibodies to pneumococci. Two hens, however, gave a positive CSR with pneumococcus II A when calcium ions were excluded (Table 1). In these two instances the positive reactions were in all probability caused by antibodies.

As it has already been shown that six different animal species are capable of producing acute phase protein there are reasons to assume that other animals are also able to do so. In order to conclude that an animal species is incapable of producing non-specific capsular swelling substance it would be necessary to use several if not all types of pneumococci in the tests.

In humans it has been shown that CRP can be produced at any time in life. In this work, patients of all ages are included and none was found incapable of producing the reactive substance. Occurrence of CRP in new born babies has been indicated by several authors. It has also been shown that CRP is not transferred across the placental barrier (14, 102, 104, 109, 120).

In the present investigation, the sera of all baby rabbits more than 24 hours old contained CxRP after an injection of more than 0.3 ml typhoid vaccine. The appearance of CxRP was caused by the stimulation of typhoid vaccine in the 1 month old rabbits and in one 2—4-hour old rabbit (given 0.2 ml typhoid vaccine) as these had a negative reaction before stimulation. It is most probable that the appearance of acute phase protein in the other animals (2—6 hours, 24 hours and 3 days old) was also caused by the dose of stimulating agent. A reservation must, however, be made as the positive reactions may be caused by other stimuli such as an infection. In this connection it is of less importance what caused the appearance of the active protein as the intention was only to show if baby rabbits could produce it or not.

The 2-hour old rabbits gave no positive reaction to 0.1 ml typhoid vaccine. It is possible that this was due to the size of the dose. When it was doubled in animals of the same age or one to two hours older, one of the baby rabbits reacted positively.

The CSR titers in the experiments on mice, hens and guinea pigs are low yet enough to make it possible to establish that these animals are capable of producing non-specific capsular swelling substance. These animals can thus be included in the same group of acute phase protein producing animals as man, monkey and rabbit.

CHAPTER 4

Different Ways of Inducing Acute Phase Protein

Acute phase protein can be induced by different stimuli both in man and animals. In 1933 Carlens and Löfström (81) used sulphur and in 1944 Hedlund (1) used several agents thought to be effective in non-specific stimulation. In 1953 Wood (147 148) used certain adjuvants for the stimulation of Cx-reactive protein response

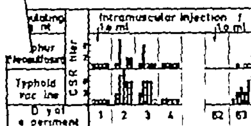
The experiments in Paper I were performed on rabbits and humans. Rabbits were injected with manganese, gold and copper salts, sulphur sterile milk, Omnadin and autoblood. The humans were given injections of manganese and gold salts, sulphur typhoid vaccine and Heptonin Tika (a liver extract drug) and given blood transfusions. The dose causing a high CxRP production in the rabbits was determined and then given to the animals at regular intervals over a period of weeks and sometimes months. CxRP was induced by all preparations except Omnadin and autoblood In man the CSR only became positive after injections of manganese salt, sulphur or typhoid vaccine

Most of the animals reacted promptly on stimulation. There was an individual response however as some animals did not react at all, not even when the doses were increased (experiment with gold salt, I p. 332 and copper salt, I p. 333) The rabbits given repeated doses of gold salt, copper salt and sterile milk seemed to react with the same degree of CxRP production on each repeated stimulation with the same agent. Those animals treated over a long period with a constant, large dose of manganese salt or sulphur showed decreasing CSR titers however

The humans given relatively much smaller doses than the rabbits, reacted in an analogous way. After repeated injections of manganese salt in eight patients a tendency towards a decrease in the ability to produce the reactive substance was observed in three of them (fig 4 e, f, g)

The results won in these first attempts to produce an acute phase protein response experimentally in animals and humans only gave a rough outline. They indicated an irregular reaction in rabbits after different sorts of stimulation. The purpose of the following experiments, performed during the years after and finished in 1955, was partly to examine the ability of different stimuli to induce acute phase protein and partly to study the various individual reactions in the animals.

As acute phase protein appears in the blood not only in response to various inflammatory stimuli but also to apparently non-infectious stimuli such as necrotic tissue, the question arose if it would be



$\varnothing$ = pos. react. with pneumococcus, type 23 B.
0 = negative reaction.
Each 0 and bar represents one animal.

Fig. 1 Five rabbits stimulated with sulphur and five with typhoid vaccine. All typhoid and four sulphur rabbits reacted with the production of acute phase protein. On second injection only the typhoid rabbits were positive. After the fourth day all samples were negative

possible to induce the reactive substance after injection of tissues from the same species and of breakdown products of proteins such as peptones and amino acids. To study the effect of necrotic tissue in vivo, lesions were induced in rabbits by freezing small areas of skin. During the experiments with tissue suspensions it was found that the presence of pyrogens caused acute phase protein production and tests were also performed to investigate this phenomenon.

In man, fever is almost always accompanied by the appearance of CRP in the blood. Experiments were therefore performed on rabbits and humans to investigate whether an elevation of temperature in itself might induce production.

Material and methods

Rabbits Adult animals weighing about 3 kg and housed in individual cages were used in all tests unless otherwise stated. These cages were kept in a building where there were no other animals. Before the experiments the animals were examined as to their state of health and acute phase protein in the blood (tested for with pneumococci types 11 A and 23 B). They were used only after they were shown to be CSR negative. After stimulation the animals were likewise tested with pneumococci types 11 A and 23 B unless otherwise stated.

Rats Adult white rats weighing about 200 g.

Blood samples taken by cardiac puncture, performed with a needle 0.8 mm in diameter. *CSR method, Sulphur preparation, Typhoid vaccine* Described in Chapter 3.

Living bacteria. Group C streptococci cultivated for 18 hours on Todd broth.

Aminosol A 3.3 % solution of amino acids and low-molecular peptides, produced by the Swedish pharmaceutical company Vitrum and used for the intravenous nutrition of humans.

Peptone Commercially available Witte's peptone. A 3.3 % solution in pyrogen-free water sterilized by fractional sterilization in flowing steam.

Saline Unless otherwise stated pyrogen-free distilled water was used for its preparation.

Sodium citrate Sterile 3 % solution prepared with pyrogen-free distilled water.

Experimental

a) *Injections of sulphur, typhoid vaccine and living bacteria*

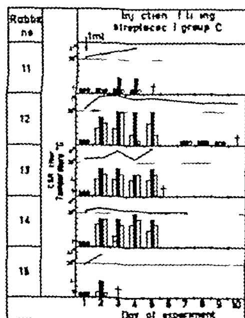
In a first experiment ten young rabbits weighing about 2.5 kg were each injected intramuscularly with 1 ml Neosulfosin. 24 hours later CxRP was shown in the blood of only three animals.

In a second experiment five rabbits were given intramuscular injections of 1 ml Neosulfosin and five other animals 1 ml typhoid vaccine. The results are shown in fig. 1. After 20 hours all the

typhoid animals had produced CxRP Of the rabbits stimulated with sulphur four were positive and one negative The titers are given in the fig It may be noted that all five typhoid rabbits and three of the sulphur rabbits reached the maximum titer in the sample drawn after 20 hours. One of the sulphur animals was negative until the fourth day when it showed a titer 1 Two months later all the typhoid rabbits were given a new 1 ml dose of typhoid vaccine intramuscularly The CSR was found to be positive for all sera 20 hours after stimulation. In four of the animals, however the titers were lower than after the first stimulation. Three of the sulphur rabbits positive on the first occasion, were given a second injection of 1 ml Neosulfoam. The protein could not now be detected in any of them 20 hours after stimulation.

Five healthy rabbits were given 1 ml subcutaneous injections of a living culture of streptococci The results are shown in fig 2. All animals reacted with fever and positive CSRs and three of them acquired high concentrations of active protein. Within a few days four of the animals died of their bacterial infections.

Further similar experiments using the above stimuli were carried out, the only difference being the size of doses. These



□ = pos. react. with pneumococcus, type 11 A.
■ = pos. react. with pneumococcus, type 23 B.
⌴ = pos. react. with pneumococcus, type 25.
0 = negative reaction.

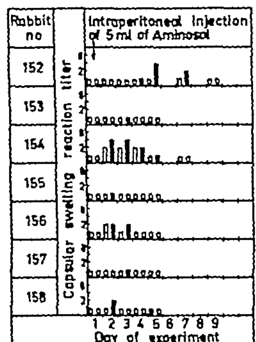
Fig 2. Five rabbits stimulated with an injection of living bacteria. All of them reacted with fever and CxRP production. Four died.

and the results are to be seen in Table 3

It is seen that a dose of typhoid vaccine of at least 0.8 ml is a good stimulus for the production of CxRP Sulphur is inferior a working dose of 0.8—1.0 ml gives more negative than positive CSRs.

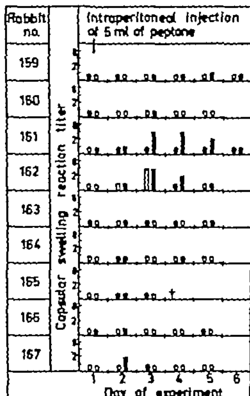
Table 3 The production of acute phase protein in rabbits given varying doses of stimulating agent

Stimulating agent	Number of positi and negative reacting rabbits						Total number of rabbits
	Dose						
	0.4 ml		0.8—1.0 ml		2.0—3.0 ml		
	pos.	neg	pos	neg.	pos	neg	
Sulphur			7	14	5	5	31
Typhoid vaccine	8	2	35	1	3	0	49
Living bacteria			8	0			8



□ = pos. react. with pneumococcus, type 11 A.
■ = pos. react. with pneumococcus, type 23 B.
0 = negative reaction.

Fig. 3 Seven rabbits given injections of solution of amino acids. Six reacted positively



□ = pos. react. with pneumococcus, type 11 A.
■ = pos. react. with pneumococcus, type 23 B.
0 = negative reaction.

Fig. 4 Nine rabbits given injections of a peptone solution. Altogether five gave positive CSR.

b) *Injections of amino acids peptone and saline* Seven healthy rabbits were each given an injection of 5 ml Aminosol and nine rabbits 5 ml injections of peptone intraperitoneally The results are to be seen in figs 3 and 4 Six Aminosol rabbits and five peptone rabbits were CSR positive.

Table 4 Rabbits stimulated with different agents

Stimulating agent	Number of rabbits		total
	positive	negative	
Aminosol	11	11	22
Peptone	10	7	17
Pyrogen-free saline	0	13	13
Ordinary saline	4	5	9
Puncturing of the peritoneal wall	0	5	5

The results of all experiments in which Aminosol, peptone and pyrogen free saline were used to stimulate the production of acute phase protein are summarized in Table 4 Half of the animals gave a positive CSR for Aminosol and about two thirds for peptone. None reacted positively after stimulation with pyrogen-free saline.

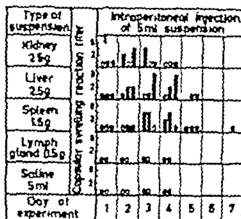
The finding that Aminosol used for the intravenous nutrition of humans, without preservative and with pyrogen-free water

a solvent, caused acute phase protein production in rabbits made further experiments with agents thought to be non-irritating or indifferent as CxRP stimulants desirable. Stimulation with ordinary saline pyrogen-free saline and the mere puncturing of the peritoneal wall of the animals was carried out. The animals were tested the first three days after stimulation and if the CSR was still positive they were tested until it became negative.

The results are to be seen in Table 4. Five rabbits received a puncture in the peritoneal wall with a coarse injection needle (1.5 mm in diameter). None of them became CSR positive. After the intraperitoneal injection of 5 ml ordinary saline, acute phase protein appeared in the blood of four out of nine animals tested. In experiments performed with pyrogen-free saline on 15 animals, none had a positive CSR.

c) *Injections of tissue suspensions*

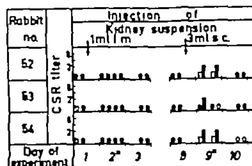
The tissues were taken from young rabbits weighing 2—2.5 kg. The animals were killed by a blow on the back of the head and then bled by cutting the throat. Dissection was performed under sterile conditions and the organs at once placed in a sterile tube. Heart, lung, liver, kidney and muscle preparations were generally made from the organs of one or two animals only. The spleen and lymph gland preparations contained organs from at least five animals. The organs were freed from fat, connective tissue, weighed and ground in a Thurmix mill. The homogeneous suspensions were washed once with pyrogen-free saline and centrifuged at low speed until the supernatant liquid was clear. This was then tested for acute phase protein content and was found to be negative



CSR performed with pneumococcus, type 23 B. Each 0 and bar represent one animal.
▮ = positive reaction. 0 = negative reaction.
Fig. 5. Groups of 2—3 rabbits given injections of different rabbit tissue suspensions.

in all cases. The organ sediments were either used immediately or kept frozen at —20 C until the following day. These were then resuspended in pyrogen-free saline. The heart, lung, liver, kidney and muscle suspensions were adjusted to 0.5—1 g per ml, the spleen suspensions to 0.2 g and the lymph gland suspension to 0.1 g per ml.

A portion of all tissue suspensions except lymph gland were digested with pepsin. The pH of each suspension was adjusted to 2.0 with HCl. A pepsin solution of the strength 10 mg/ml was made up using a preparation with a proteolytic activity of 1:10,000 (Parke Davies & Co.). The tissue suspension and pepsin solution were mixed in the proportion 9 to 1. The tissue-pepsin mixture was then placed in an incubator at 37°C for 2 hours. After about 2 hours at room temperature the pH was adjusted to 7.0. Control tests were made with two pepsin solutions, one containing 10 mg/ml saline and the other 1 mg/ml saline. Two rabbits were first injected



The animals tested twice

□ = pos. react. with pneumococcus, type 11 A.
■ = pos. react. with pneumococcus, type 23 B.
0 = negat. reaction.

Fig. 6. Three rabbits injected with 1 ml kidney suspension (1 g/ml) intramuscularly and later on with 3 ml subcutaneously. Only the higher dose stimulated acute phase protein production.

with 1 ml of the weaker solution and three days later with 1 ml of the stronger.

In the first experiment 13 animals were used as seen in fig 5. Groups of 2—3 animals were injected intraperitoneally with saline, and kidney, liver, spleen and lymph gland suspensions. After about 20 hours two of the animals injected with kidney and two injected with liver were positive. On the 3rd day two injected with spleen reacted positively. No acute phase protein was found in the blood of animals treated with lymph gland tissue or saline.

Fig. 6 represents an experiment on three animals where kidney tissue alone was injected. A 1 ml intramuscular injection caused no positive reaction but a 3 ml injection given subcutaneously did.

A similar experiment is shown in fig 7, this time using muscle suspension. As seen, no animal reacted positively to the 1 ml intramuscular nor the 3 ml subcutaneous injection. When the animals were given injections of liver suspension, on the other hand, all became positive.

Fig. 8 refers to an experiment on two animals given injections of different tissue suspensions. Each was first given a 3 ml subcutaneous injection of lung suspension. One of them gave a strong positive reaction. This same rabbit also showed itself to be positive after injections of pepsin-digested lung, heart, liver and kidney. The other animal gave only weak positive reactions after injections of pepsin-digested lung and kidney.

Four healthy CSR negative rabbits were bled. The blood was at once mixed with sodium citrate to prevent coagulation. About six hours later the samples were each injected into four healthy rabbits, each animal given 2 ml blood intraperitoneally. A fifth animal was injected with 1 ml sodium citrate. Two

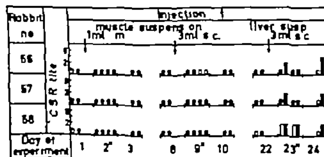
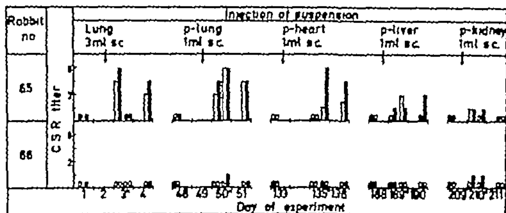


Fig. 7. Three rabbits injected with muscle suspension (1 g/ml) once with 1 ml intramuscularly (i.m.) later with 3 ml subcutaneously (s.c.) and still later with 3 ml liver suspension (1 g/ml) s.c. Only after the injection of liver did acute phase protein appear.

The animals tested twice

□ = pos. react. with pneumococcus, type 11 A. ■ = pos. react. with pneumococcus, type 23 B. 0 = neg. react.



The animals tested t ice

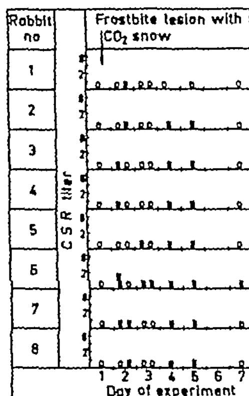
□ = pos. react. with pneumococcus, type II A. ■ = pos. react. with pneumococcus, type 23 B.
0 = negative reaction. p- = pepsin-digested.

Fig. 8. Two rabbits treated several times with subcutaneous injections of various tissues (0.5 g/ml). *The different reactibility of the two animals is seen.*

Table 5. Number of rabbits giving positive and negative CSRs with pneumococcus type 23 B after stimulation with injections of tissue suspensions

Amount injected	1.0 ml s.c.		1.0 ml i.m.		3.0 ml s.c.		5.0 ml i.p.		Total number	
Suspension	pos.	neg.	pos.	neg.	pos.	neg.	pos.	neg.	pos.	neg.
Heart	7			3	4	2	2	1	13	6
Lung				2	2	4			2	6
Liver			1	2	5	4	3	5	11	11
Kidney				3	6		6	4	12	7
Muscle				3	2	5	2	1	4	9
Spleen			1	2	2	1	6	2	9	5
Lymph gland							2	3	2	3
Blood							2	2	2	2
Pepsin-digested heart	3	6							3	6
Pepsin-digested lung	11	4							11	4
Pepsin-digested liver	3	4							5	4
Pepsin-digested kidney	6	6							6	6
Pepsin-digested muscle	1	2							1	2
Pepsin-digested spleen	0	2							0	2
Pepsin dilution *(1 mg/ml)*	0	2							0	2
Pepsin dilution *(10 mg/ml)*	1	1							1	1
Pyrogen-free saline	0	1			0	3	0	9	0	13

s.c. = subcutaneously i.m. = intramuscularly i.p. = intraperitoneally 2 ml.



■ = pos. react. with pneumococcus, type 23 B.
0 neg. react. with pneumococcus, type 23 B.
Fig. 9 Eight rabbits with frostbite lesions induced by the application of CO ice to the skin. All animals were later found to be CSR-positive.

of the blood rabbits showed a positive CSR after 70 hours (Table 5). The other two and the citrate rabbit were negative.

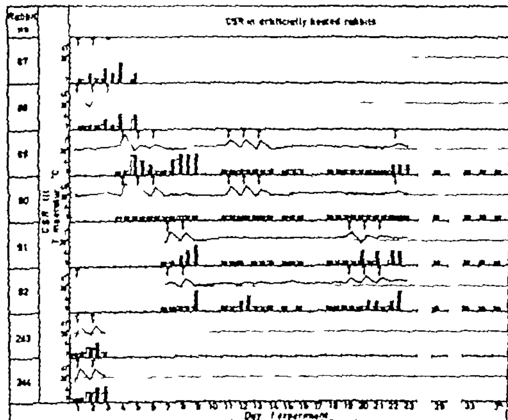
A further series of experiments with injections of various tissues were performed. The results were on the whole in agreement with those presented above. They are therefore not described in detail but only presented in condensed form in Table 5 where it is to be seen that all rabbit tissue suspensions tested were able to induce acute phase protein production. The weak pepsin solution, the amount of pepsin injected corresponding to that in the tissue experiments, induced no CxRP production. A solution 10 times stronger however induced a weak positive reaction of titer 1 in one control rabbit.

d) Artificially Induced Skin Lesions in Rabbits and Rats

Eight rabbits and ten white rats were shaved over an area of about 5 × 5 cm on one buttock two days before the lesions were induced. Before experiments were begun it was made certain that the shaved areas were free from all injury. CO ice was applied to the shaved patches over a circular area of diameter about 2 cm for 30 seconds. This caused an immediate frostbite. On the following day erythema and swelling was to be seen on the site of application. The lesion healed with the formation of a scab as after a superficial scrape. The wound, however, showed signs of secondary infection on the 3rd or 4th day with redness and slight secretion. The rabbits were bled once before the freezing, twice on the 2nd and 3rd days and then once a day until they became negative. The rats were only bled once a day. All sera were examined with pneumococci types 11 A, 23 B and 28.

Seven of the eight animals gave a low-titer CSR by the day after (fig 9) three of them as early as after sixteen hours. It is noteworthy that in some rabbits (nos 1, 2, 3, 4, 5, 7 and 8) the reactive substance disappeared on the 3rd day of experiment — the morning sample taken from rabbit 5 was positive but by the afternoon it was negative. In animals 2, 3, 4, 5, 7 and 8 the reactive substance was again found on the 4th or 5th day of experiment. No. 6 was positive on all occasions from the 2nd day onwards. On the 7th day all animals were negative except no. 6.

All rats proved to be CSR-positive



⌒ = incubation. □ = pos. react. with pneumococcus, type II A. ■ = pos. react. with pneumococcus, type 23 B. 0 = negative reaction.

Experiment on rabbits 87 and 88 performed in Nov. 1954. Experiment on rabbits 89–92 performed from Jan. to Mar. 1955. Experiment on rabbits 243 and 244 in Aug. 1960.

Fig. 10. Eight rabbits heated for 6 ½ hrs in an incubator (37° C). The elevation of temperature in all eight and the appearance of acute phase protein in seven animals is to be seen.

with pneumococci types II A, 23 B and 28 before the experiment. After the application of CO ice the CSR titers were of approximately the same magnitude as before. All the rat sera were also CSR-positive when calcium ions were excluded by the addition of sodium oxalate to the reaction mixture (VII p. 219). These titers were of the same or of a one step lower magnitude.

) Artificial Elevation of Temperature

In the considerable clinical material in *Paper II* it was found that CRP was present in the sera of all cases with a temperature above 38°C. Patients with only a slight elevation of temperature were often negative. In order to find out at what stage in the rising temperature CRP appears and how quickly after induction it can be demonstrated in the blood the experiments presented in Paper III were performed.

Fever was induced by a suspension of formalin-killed Aerobacter aerogenes administered by continuous intravenous

drip. It was possible to induce CRP production in all cases. After a fever period of 10—20 hours CRP could as a rule be demonstrated in the blood, the maximum titer appearing 18—22 hours after the beginning of administration. The white blood cell count and sedimentation rate were also measured. It appeared that the behaviour of temperature, white blood cell count, CRP and sedimentation rate after experimentally induced fever was similar to their behaviour in cases of myocardial infarction.

During these experiments the influence of sodium salicylate medication on the production of CRP and on the changes in the other routine blood measurements was also studied. The results are presented in Paper IV. It was demonstrated that CRP appears at the earliest about 12 hours after administration of vaccine. The sodium salicylate exerted no influence on the production of CRP in these experiments.

From experiences in the clinic and the above-mentioned experiments the question arose if an elevation of temperature in itself might induce the production of CRP. The following experiments were performed on rabbits which were heated for several hours until their temperatures rose. An analogous experiment was also performed on humans.

Experimental. Rabbits. Eight healthy adult rabbits were heated in an ordinary incubator (37 C) for 6 1/2 hrs. The experiment was performed on three different occasions as seen in fig. 10. The animals were placed in the incubator at 9 a. m., removed at 3 30 p m. and replaced in their cages for the night. At 8.30 a.m. and 3 30 p m. each day their temperatures were measured and they were bled by ear puncture. The procedure was repeated three times for rabbits 87 and 88, seven times for 89 five times for 91 and 92 and twice for rabbits 243 and 244. As seen in fig. 10 all animals reacted with an elevation of temperature of 1—2° C. The morning after incubation temperatures had returned to normal. All rabbits except no 90 became CSR positive. The reactive protein was shown 17 hours after the first heating in five rabbits (87, 88, 89, 92 and 244). In rabbits 91 and 243 there was a very quick reaction, their blood becoming positive immediately after the first period of incubation. Rabbit 90 was incubated as the others several times. This rabbit, however, in spite of an adequate fever reaction, remained negative during the whole experiment.

Humans. Five patients treated in the Neurological Clinic at Serafimerlasarettet for chronic luetic diseases were examined for their ability to produce CRP when subjected to a temperature of about 40°C in an ultrapandorus apparatus. On each occasion the patient was heated to about 40°C for 2—3 hours. One patient was heated once, one twice, one four times and two patients five times. The blood samples were drawn just before heating, six hours after fall of temperature and the morning after heating. All blood samples were negative.

Discussion

The results of all these experiments indicate that different agents can be used for the induction of acute phase protein in rabbits as well as in humans. Inorganic compounds, dead and living bacteria, amino acids, peptides, tissue suspensions of the same species and tissue necrosis are all able to induce production.

An individual response was already observed in the first experiments on rabbits. Most of the animals reacted promptly on stimulation and continued to do so even after renewed stimulation with the same agent. Some animals however did not react at all, not even when the doses were increased. This varying reactibility in the individual rabbits must be taken into account. Before starting an experiment it may be of value to know that the animals are on the whole able to produce acute phase protein after injection of the stimulus in doses which are practically applicable otherwise later results may be incorrectly interpreted. The individual acute phase protein reaction has been of practical use in the preparation of CRP antisera. Wood (147) stimulated only high CSR titer rabbits with human CRP as it was shown that these animals also produced the best amounts of CRP antisera.

By repeatedly injecting large doses of manganese salt the animals showed decreasing CSR titers (I). An interesting and perhaps analogous observation was made by Montella and Wood in 1957 (97) who found that thorotrast (colloidal thorium dioxide in dextrin) caused the appearance of CxRP in the blood of rabbits. On repeated injections of the agent, however the amount of CxRP produced gradually diminished until little or none could be detected. The authors believed that the reticulo-endothelial system was effectively blocked by the thorotrast and thus the further production of CxRP impeded. They also stated that another explanation might be its direct toxic effect on cells other than those of the reticulo-endothelial system. The decreasing responses after treatment with manganese salt for a long time (about four months) referred to in Paper I may perhaps, be for the same reason. The thorotrast, however was given intravenously and the manganese salt intramuscularly. A fact worth noting is that the two substances able to cause such a reduction are both inorganic metallic oxides.

The experiments using sulphur typhoid vaccine and living bacteria indicate that there is a greater possibility of attaining acute phase protein production after stimulation with relatively small practicable doses of typhoid vaccine or living bacteria than with sulphur. Typhoid vaccine was thus most often used to stimulate production experimentally. It has also been used by Anderson and McCarty (9) and Stollerman, Glick and Anderson (135). In spite of the fact that injections of living bacterial suspensions give a high yield of CxRP such an agent cannot be used in routine experimental work — the animals usually fall severely ill and most often succumb. Experience from earlier experiments (I) that some animals do not react at all and that repeated doses of the same stimulus in those that do react often induce the highest titer on the first injection was confirmed. When using typhoid vaccine, such a reduced effect may be explained by antibody production but not when manganese or sulphur were used.

The solutions of amino-acids and peptides used in these experiments were able to stimulate the production of acute phase protein in the rabbit. This is clearly exemplified in the first experiment (figs. 3 and 4) and in Table 3. The Aminosol reaction in rabbits may possibly be a parallel phenomenon to the findings of Berg (16). After injections of Aminosol intraperitoneally in rats he found a slight cell reaction either leuko-

cytal or more often mononuclear in the omentum. In several of the animals there was a considerable increase in the number of plasma cells.

From the results of the "tissue" experiments it is not possible to say that one organ is more apt to induce a response than another. The purpose was only to see if acute phase protein appeared or not. It seemed, however, as if heart, kidney and spleen suspensions produced positive reactions more easily than the other organ suspensions.

An analogous experiment was made by Wood and Montella in 1957 (151) who found that rabbits injected with rabbit CxRP produced CxRP. They supposed this was a unique property of the CxRP. In the light of experiments presented here *it is most feasible to regard the* CxRP production after stimulation with CxRP to be a phenomenon analogous to the production of CxRP after stimulation with protein or with different tissues of the same species. Hokama et al. got a "biphasic" CRP response after primary immunization of rabbits with bovine albumin or human γ-globulin (61).

All tissue suspensions tested induced CxRP. From the clinic it is well-known that infarct of heart, lung, kidney and spleen induces CRP production. In the experiment with artificially induced, non-infectious skin lesions in the rabbit it was possible to demonstrate that localized necrosis in the skin is also accompanied by the appearance of CxRP. The appearance of the substance on the 2nd day and then its disappearance between the 3rd and 4th days may possibly be explained by its being caused on the first occasion by tissue damage and on the second occasion by secondary infection. As the rats had specific antibodies to the pneumococci used as test agents it was impossible to show if acute phase protein appeared in their blood.

The induction of acute phase protein in rabbits merely by an elevation of their temperature by heating in an incubator is a type of reaction quite apart from others inducing its formation. Much can be speculated as to its mechanism. The possibility of false positive reactions may be excluded. The experiments were very easy to perform, the cardiac punctures were made without complications, the animals showed no sign of infection, were in good condition during the whole experiment and their temperatures quickly returned to normal after they had left the incubator. The experiments were repeated three times with different animals, all with the same result.

It has been shown that sterile operations induce CRP production (28, 113). The puncture through the chest wall may be regarded as a miniature sterile operation. The cardiac puncture method of drawing rabbit blood has been widely used in all these experiments. If the blood is drawn when the rabbit is quiet, held in the correct position and the puncture performed with a proper technique there is no risk of hurting the animal. In very few instances has acute phase protein production been observed after cardiac puncture, and then only when complicating hemorrhages have occurred in the thorax with destruction of pericardial, pleural or lung tissue. In this connection it is also worth noting that the mere puncturing of the peritoneal wall with a coarse injection needle (1.5 mm) did not cause enough destruction of tissue to induce production. The puncture in this experiment was far larger than a cardiac puncture which is performed with a much finer needle (0.8 mm).

The heated humans were all neg tiv It is interesting to not that as earl a 1933 in the first clin al evaluation of CRP Ash, u ng the C-polysaccharide test, discussed f th fever tself may produce some physico-chemical change in the blood responsible for the pre cip tation" (10)

Blood transfusion in humans did not induce CRP production in the two instances referred to in Paper I Had the sample been taken some twenty hours later the chances of obtaining a positive reaction would probably have been greater Often since during the course of this work, high titer reactions have been observed in the clinic after blood transfusions followed by fits of shivering and fever Knights et al. have indicated the appearance of CRP after blood transfusions (65 66) Rabb t heart blood obtained by puncture and directly injected intramuscularly in the same animal induced no formation of acute phase protein, not even when the blood had been defibrinated with glass pearls, chilled and then injected intramuscularly (I) In another experiment it did prove possible to induce production in rabbits after injection of rabbit blood. Of four rabbits injected with a small amount of rabbit blood from other animals two produced acute phase protein (Table 5)

Attempts have been made to evaluate the CRP test as a screening procedure for blood donors and as a basis for predicting so-called minor non-hemolytic transfusion reactions in recipients of blood" by Knights et al. (65) All of their patients who experienced chills after transfusion developed a positive CSR. The majority of these patients first showed positive reactions on the 3rd and 5th post-transfusion days. The uthors considered that this possibly epresents a type of immune reaction"

The *appearance time* of CRP was shown in Paper III to be 15—21 hours after the beginning of vaccine administration. In the following experiments (IV) the CRP was found to appear at the earliest about 12 hours after the beginning of stimulation. During this work there have been many opportunities of studying the appearance time. The shortest found in the clinic was 8 hours in a patient with a myocardial infarction. In the laboratory single injections of typhoid vaccine have been used to induce CxRP formation. The appearance time in rabbits has most often varied between 16 and 18 hours. Many statements have been published about it. As early as 1941 Carlens (28) demonstrated CRP 24 hours after operation. Anderson and McCarty (9) found t to be 18 hours in humans and 12—18 hours in rabbits. Björnesjö, Werner and Odin (19) demonstrated CRP 12—18 hours after operation. The shortest time was shown by Stollerman, Glick and Anderson (135) who demonstrated CRP 6—12 hours after a single intravenous injection of typhoid vaccine. Such a short time has also been demonstrated in this work. On artificial heating two rabbits showed CxRP in their blood as early as after 6 hours (fig 10)

The CSR is useful for detecting reactions to different stimuli and is very sensitive. Sometimes t may not be easy to differentiate between several possibl causes of a positive reaction. It is of the utmost importance to use healthy animals and to make a control test before the stimulating agent is given. The animals must be kept isolated and protected from nosocomial infections and several of them must be used for each test as some may be bad producers.

CHAPTER 5

Biochemical and Biological Properties

The site of origin and function of CRP is unknown and much speculation has been made as to its significance. During the course of this work experiments have been performed to obtain information about its composition by electrophoresis and cross-absorption and about its presence in leukocytes, lymphocytes and lymph.

a) *Electrophoretic experiments* (III V VI)

Questions have often arisen about the chemical nature and biological function of CRP The early physico-chemical studies did not give conclusive results (81 107 In an attempt to arrive at more accurate data Hedlund, Frisk and Bucht, in 1948, (III) made free electrophoretic studies on sera obtained after experimentally induced fever in humans. In the study published in this paper the changes in electrophoretic sera patterns were followed during the course of induced fever in two patients. A relative decrease in the albumin content and a relative increase in the globulins was revealed, the latter almost entirely due to increased alpha-globulins. It was not possible to localize CRP in the electrophoretic picture This negative finding does not agree with the supposition made in Paper II that the increase [of globulins seen in [illegible] processes] is probably in part due [illegible] ute phase protein" Against the background of today's knowledge it is understandable that it was not possible to localize the CRP with the method used It was remarked that the reason why acute phase protein could not be located in the electrophoretic diagram is probably that it is present in the blood in such small quantities that it cannot be demonstrated by this method" Similar findings were made by Wood et al. (149) and by Müller et al. (101) In free electrophoretic studies on an acute phase serum before and after removal of the CRP they found no significant difference in the patterns They considered this not so surprising as sera giving maximal precipitation with antiserum to CRP contain only 0.35 mg CRP per cc of serum" The situation altered when serum could be analysed with the zone electrophoresis technique which permits the withdrawal of small samples for direct analysis. In Paper V a preliminary report by Hedlund and Brattsten was given on an electrophoretic examination of human acute phase serum with the aid of continuous zone electrophoresis according to Svensson and Brattsten 1949 (136) Pooled sera from two patients were investigated and tested for CRP by the CSR method with pneumococci type 23 B. The reactive substance was found to be situated in the gamma-globulin fraction.

These first results invited the further experiments presented in Paper VI. Five CSR positive human sera from typical cases of acute infection were fractionated. The continuous-working zone electrophoresis apparatus described by Brattsten 1955 (21) was used. The validity of the results was checked by analytical electrophoresis tests in free solution and on filter paper. The C-reactive substance was tested by Löfström's CSR method and, for comparison, each CRP-positive sample was also tested with CRP antiserum.

The CRP was found to migrate with the gamma-globulins. The highest titers were found in the fractions which corresponded to the maximum of the gamma-globulin distribution curve.

The results of the electrophoretic fractionation reported in Paper VI were in general agreement with the findings of Wood, McCarty and Slater in 1954 (149). In their starch column experiments, however, the CRP was shown to migrate as a fast gamma-globulin. All the experiments in Paper VI showed a slower migration rate. These discrepancies were discussed with regard to sorption by the starch medium, ionic strength and pH. It was considered that they might be more related to differences in pH than to any sorption of the active substance by the medium used or its ionic strength.

Since the publication of the two papers mentioned, several electrophoretic studies on CRP have been performed (25, 26, 44, 48, 101, 103, 105, 109, 116, 124, 155). Philipson and Tveterås (109) used a cellulose medium in vertical columns and found the reactive substance between the gamma and beta-globulins. Using continuous-flow paper electrophoresis and immuno-electrophoresis respectively, Rowntree et al. (116) and Bustamente et al. (25, 26) found the CRP to be located in the gamma-globulin fraction. On immuno-electrophoresis of human acute phase serum, Nishimura (103) found three components. One was located in the fraction between the beta and gamma-globulins and the other two in the alpha$_1$-globulin fraction. Hansen, Marner and Ejby Poulsen in free electrophoresis found CRP to migrate with the beta-globulins although small quantities were also demonstrable in the alpha and gammma-globulins (48).

During the study described in Paper VI it was shown (p. 220) that the addition to half saturation of ammonium sulphate to the CRP-containing gamma-globulin fraction caused a precipitate of all the gamma-globulin present and a liquid phase in which the CRP activity was unchanged.

b) *Cross-absorption experiments* (VIII)

With the aid of cross-absorption experiments on human acute phase protein described in Paper VIII it was possible to show that it consists of at least two components.

When acute phase sera were mixed with suspensions of pneumococci type 23 B or 27, centrifuged and the clear supernatant liquid tested with CRP antiserum, no precipitate was visible. All of the reactive substance had thus been absorbed by the respective pneumococcal suspension. In an analogous absorption test it was shown that CRPA absorbed all the substance which gave a positive CSR with types 23 B and 27. Polysaccharides produced from types 23 B and 27 were also able to absorb all the capsular swelling substance but not all the substance which reacted with CRP-antiserum. Like the CRPA, the intact pneumococcal cells of types 23 B

Table 6. Results of experiments with rabbit lymph and lymphocytes

Rabbit No.	Solution tested	CSR-titer with pneumococcal type			
		11 A	23 B	27	28
18	Serum	2	4	0	0
	Lymph	0	0		
	1st washing	0	0	0	0
	2nd washing	0	0	0	0
	Sîmms solution	0	0		
9	Serum	2	4	0	0
	Lymph	0	0		
	1st washing	0	0		
	2nd washing	0	0		
	Sîmms solution	0	0		

and 27 possess the property of absorbing all CRPA reacting substance. Some factors present in the pneumococcal cell might thus be lacking in the polysaccharide. It was concluded from these results that the CRP in human serum consists of at least two components.

This finding has been confirmed in serologic and fractionation studies by other authors. In a study on CRP Fishel, Vedros and Rothlauf (38) said that "it has been assumed that one protein present in acute phase serums was responsible for all these serologic manifestations and that each test was measuring the reactivity of the serum in terms of this single substance". They were unsuccessful in removing the CRPA reactant by polysaccharide absorption and their ammonium sulphate fractionation results suggested the presence of two components in acute phase serum.

By agar diffusion, the same authors using the Ouchterlony technique (106) modified by Wadsworth (144) found that CRP of acute phase serum possessed three antigenic components regardless of the illness which caused its production. They confirmed the findings of Libretti et al in 1955 (74) who, using the Ouchterlony technique modified by Halbert (47) had demonstrated three distinct bands when purified CRP was allowed to diffuse in agar against rabbit CRPA. In 1959 Nishimura (103) using the "double diffusion technique" found the CRP in human serum to contain "up to three antigenic components".

c) *Experiments with leukocytes, lymphocytes and lymph*

CRP has been demonstrated in serum and exudates (79 81 87 138). In this work attempts have been made to see if the CRP could also be obtained from lymph, lymphocytes and leukocytes. The experiments on lymph and lymphocytes were performed using rabbits while the leukocytes were taken from humans in the acute phase of disease.

Experimental

Lymphocytes. Two rabbits weighing 2.5 and 3.3 kg were given an intramuscular injection of 1.0 ml 12 hour old Todd broth culture group C streptococci. Two days later the animals were operated on using a technique described by Wenlén (145). Lymph was collected from the thoracic duct and blood drawn by cardiac puncture. After preparation of the thoracic duct the animals were each given 1 ml 0.5 % heparin subcutaneously. 16 ml lymph were taken from one of the rabbits and 5 ml from the other. This was then centrifuged, lymph plasma removed and the sediment consisting of lymphocytes washed twice in an amount of normal saline equal to the plasma removed. The washed lymphocytes were placed in 2 ml Sîmms

solution containing 100 i.u. penicillin and 50 gamma streptomycin per ml and incubated for 48 hours at 37° C in a roller tube rack.

The rabbit serum, lymph, 1st and 2nd washings and Simms lymphocyte solution were tested for CRP content.

The results are presented in Table 6.

The rabbits stimulated with living streptococci produced acute phase protein as is seen from the positive reacting sera. Lymph collected at the same time and saline washings, however, gave a negative CSR. Even after cultivation of the lymphocytes in Simms solution none was found to be present.

Leukocytes. The experiments on human leukocytes were performed as follows:

Blood was drawn by venal puncture from two patients (1409/55 and 1489/55) treated for acute pneumonia in the Hospital for Infectious Diseases in Stockholm. Each blood sample of ~5 ml (in the following designated *O* and *L*) was collected in a glass tube, the inner surface of which having been coated with a layer of paraffin and containing 0.1 ml of 1 % Heparin Vitrum. The tubes were immediately placed in crushed ice. 1 ½ hours later they were centrifuged at +4° C for 30 mins at 3,500 r.p.m. This gave a yellow layer of leukocytes floating on the plasma about 2 mm thick in both tubes, the red corpuscles lying below. The plasma was then carefully drawn off with a fine pipette until the yellow leukocyte layer lay just over the centrifugate of red blood corpuscles. Two drops of protamine hydrochloride (1 % sterile solution of protamine hydrochloride, Vitrum) were added to the yellow layer. This caused an almost immediate coagulation of the layer into a fairly firm elastic membrane which was then lifted out of the tube with two

Table Results of experiment on human leukocytes

Solution tested	CSR titer with pneumococci type 27
Plasma O	32
Plasma L	32
Solution of white cells O	0
Solution of white cells L	0
Plasma O 1.0 ml + Solution of white cells O 0.03 ml (I)	32
Plasma L 1.0 ml + Solution of white cells L 0.03 ml (II)	32
I after incubation at 37° C for 1 hour	32
II after incubation at 37° C for 1 hour	32
I after room temp. overnight	32
II after room temp. overnight	32

Pasteur pipettes and washed in saline. The volumes of the membranes were 0.52 ml and 0.3 ml. The leukocyte membranes now free of red corpuscles were placed in test tubes and 8 drops (= 0.17 ml) of double-distilled water added to each. The mixtures were refrigerated at −20° C until frozen, thawed again and then refrozen and kept at −20° C overnight. In the morning the leukocytes were crushed in a mortar and 1 ml Ringer solution added. These suspensions were centrifuged until a clear supernatant liquid was formed (below called "solution of white cells O and L"). This was mixed with plasma as seen in Table 7.

The results are to be seen in Table 7. Both plasma O and L had a high CRP titer 32. CRP could not be shown in the solutions containing crushed leukocytes O and L. The CRP titer of the plasmas O and L was not changed by the addition of the respective leukocyte solutions.

Discussion

The rabbit lymph did not contain acute phase protein when there was a CSR titer 4 in the serum with pneumococcus type 23 B. Thus there was clearly no parallelism between the content in serum and lymph. However only when experiments have been performed using animals giving maximum serum CRP titers may the question of the appearance of acute phase protein in the lymph be fully answered.

It was not possible to show capsular swelling substance in the rabbit lymphocytes or in the human leukocytes. The human plasmas had a very high CRP content. Two possibilities may be considered that the blood corpuscles do not contain a sufficient amount of CRP to be detected by the CSR or that they might contain a CRP impeding substance The last possibility seems improbable as the plasma mixed with a solution of crushed white blood cells had the same CSR titer as before mixing

Several attempts have also been made to find CRP in different organ tissues Liver lung heart, kidney spleen and muscle tissue from rabbits with a high CSR titer have been ground diluted with small portions of Ringer's solution (Ca) until semi-liquid, centrifuged, and the clear supernatant tested for CRP The results have always been negative

CLINICAL STUDIES

CHAPTER 6

The Appearance of CRP in Various Diseases (II)

The results published in Paper II in 1947 gave a survey of the pathological conditions in which CRP appears. A large number of patients, some 2,000, treated at St Erik's Hospital in Stockholm had been examined. The presence of CRP was recorded in a variety of diseases: pulmonary and acute respiratory diseases, acute abdominal diseases, diseases of the kidney and urinary tracts, rheumatic fever and rheumatoid arthritis, cardiovascular diseases, diseases of the digestive system, metabolic and endocrine disturbances, diseases of the blood, some virus diseases, malignant and benign tumours, and a few diseases of the skin.

Lung diseases and acute upper respiratory tract infections

The behaviour of CRP in acute cases of infectious disease was exemplified by the typical course of CRP in acute pneumonia. CRP reaches its maximum during the first days, then gradually decreases and disappears after 8—10 days. Relapses and complications can be revealed by its reappearance. In all, 364 patients with respiratory infections were examined. Of these, 254 patients suffered from *acute pneumonia* and all but 2 were CRP-positive. It is noteworthy that the two negative cases suffered from pneumonic congestion. Most of the *acute upper respiratory infections* were negative: 23 out of 36. When such an infection was complicated by sinusitis the CSR was most often positive. Today we know that a *purulent sinusitis* almost always induces CRP production and the CSR test is a good clinical help in revealing this complaint. Most of the *asthma* patients, 12 out of 15, gave negative CRP reactions. Every patient suffering from *acute pulmonary tuberculosis*, 13, was positive, while those in the convalescent stage, 6, were negative.

The appearance of CRP in diseases of the respiratory tract and lungs has been studied by many authors (10, 28, 43, 79, 80, 81, 103, 115, 125, 143, 153). It has been made clear that infections caused by bacteria more often induce CRP production than those caused by viruses (100, 115, 133, 146, 153). Early on, Löfström found that CRP did not occur in certain cases of virus disease (81). Hedlund (II), Roantree and Rantz (115), Yocum and Doerner (153) and Stern and Smith (133) examined some cases of virus infection and did not find CRP as consistently as in bacterial infection. As in this survey (II), many investigators have noted the appearance of CRP in some bronchial

asthmatic patients (1 63 65 75 115 131 139 153) The importance of chest X-ray in asthma cases with a positive CRP test has been pointed out (139) Regarding pulmonary tuberculosis, the findings here (II) have been confirmed (43 65 115 129 143 153) as CRP is most often shown during the acute stages of the disease.

Acut abdominal diseases The total number of patients examined was 708. Such acute abdominal disorders as acute pancreatitis, abdominal abscesses and peritonitis were always accompanied by a positive CSR. Patients with acute salpingitis were also CSR-positive

The 175 patients operated on for *acute appendicitis* indications were specially tested for the appearance of CRP It was thought that the CSR might perhaps serve as a good diagnostic guide in such cases. Of 65 patients with typical acute inflammatory appendiceal changes only 31 (48) were CRP positive. 19 cases with little or no microscopical changes ga e negative reactions.

The clinical picture in *diseases of the biliary ducts* is often obscure The deter mination of the CRP is of value in deciding whether there is an acute in flammation. This was shown in 30 operated cases. All patients with acute inflammatory changes in the biliary ducts 14 were CSR positive Negative cases 16 revealed only stones and chronic changes in the walls of the gall bladder Attacks of biliary dyskinesia, 11 were not followed by the appearance of CRP

The appearance of CRP in patients with acute appendicitis has been studied by Knights, Hutchins and Morgan (65) who only found a pos tive reaction in one out of 6 patients with appendicitis. Selman and Halpern (125) give an account of 10 cases of ppendicitis, only one of which showed a positive reaction None of these authors however presents results of histo-pathological investigation. Ref erences to diseases of the biliary ducts will be discussed in Chapter 8.

One hundred and thirty-five patients suffering from *diseases of the kidney and urinary tracts* were investigated. Those with acute cystopyelitis 15 all showed CRP production while cysti tis with minor symptoms, 6 nephro-lithiasis, 19 nephrosis 5 acute nephritis 22, chronic nephritis 57 and uraemia 6 were not accompanied by the appearance of CRP In cases with fever later discovered to be cysto-pyelitis or pyelonephritis, the CSR was found useful for diagnosis. These dis-orders are most often accompanied by CRP production.

The results won here have been con-firmed by others. In ten cases of acute pyelonephritis, Yocum and Doerner (153) found five to have a positive CRP test while none of five chronic pyelonephritic patients showed a positive reaction. All 15 patients with acute cystopyelitis quoted by Selman and Halpern (125) reacted positively as did also 9 of 10 quoted by Roantree and Rantz (115) The results for the other diseases of the kidney and urinary tract presented in Paper II have also been confirmed by others (6 43 115 125 142 153)

Rheumatic fever and rheumatoid arthritis In 28 patients suffering from acute rheumatic fever there was a high titer CSR during the active stage of the disease Of 128 cases of *rheumatoid arthritis* examined, 94 were CRP positive. For the majority of the negative cases the disease was considered to be dormant after temporary healing It was noted that this disease does not behave in the same way as rheumatic fever as regards

CRP formation. In rheumatoid arthritis, CRP is most often present for a long time when the disease is active. Even after the temperature has fallen, sedimentation rate sunk to 10—15 mm and the patient feels quite well, it is often possible to show a low CRP titer as an expression of continued activity of the disease. In the most acute stage of rheumatic fever CRP appears in high titer. When the patient improves after salicylate treatment the CRP disappears. On exacerbation, spontaneous or provoked by treatment with sulphur, non-specific stimulation, tonsillectomy (Hedlund I 53) and the like, the CRP reappears.

Hill in 1951 (59) came to a somewhat different conclusion as he stated that "rheumatic fever differs from rheumatoid arthritis: occasional undoubtedly active cases of rheumatoid arthritis do not give a positive reaction".

Using the C-polysaccharide precipitin test, Ash (10) as early as 1933 could show the appearance of CRP in rheumatic patients. Anderson and McCarty in 1950 in a study on acute rheumatic fever (8) concluded that the presence of CRP in the blood is perhaps the most sensitive indication of rheumatic activity. This is in agreement with the earlier findings of Paper II not only in cases of rheumatic fever but perhaps even more so in cases of rheumatoid arthritis. Later papers concerning the appearance of CRP in rheumatic disease also confirm the findings in Paper II (5, 6, 18, 24, 27, 29, 30, 31, 32, 33, 35, 36, 39, 60, 64, 65, 69, 73, 77, 88, 90, 91, 92, 93, 96, 99, 111, 115, 117, 121, 125, 126, 127, 134, 137, 143, 146, 150, 153, 154). Two great advantages of the CRP test in revealing rheumatic activity are its high degree of sensitivity and the absence of CRP in a healthy serum.

The effect of *salicylate treatment on CRP production* in cases of rheumatic fever was studied in Paper II. Apart from a general improvement after treatment there was also a disappearance of CRP. This was also later experienced by Anderson and McCarty (8) and others (60, 126). The effect is analogous to that seen after cortisone and ACTH treatment which has been extensively studied by many, especially in cases of rheumatic fever (23, 31, 73, 90, 91, 111, 121, 126, 134, 154).

The studies referred to in Paper IV were performed in an attempt to see if treatment with sodium salicylate might retard artificially induced CRP production in man. These experiments established that it was not possible in this way to suppress the production of acute phase protein induced by continuous intravenous administration of a vaccine. These findings were in accordance with those of Stollerman, Glick and Anderson (135) who induced CRP in human subjects by injecting typhoid vaccine. During this procedure they administered cortisone, ACTH and salicylates. There was no significant alteration in the time, intensity or duration of the C-reactive response in any of their patients. Similar results were noted in analogous experiments on rabbits given subcutaneous injections of living pneumococci. The authors stated that "the disappearance of C-reactive protein from human blood during antirheumatic therapy with adrenocortical hormones or with salicylates is secondary to suppression of the inflammatory process rather than a primary effect of these agents upon the metabolism of the C-reactive protein".

Cardiovascular disease. A total of 245 patients were examined. All cases of *myocardial infarction* (47) were positive as

distinct from cases of *angina pectoris* 11 *cardioarteriosclerosis* 50 and *essential hypertension*, 68 which were negative The majority of patients treated for *congestive heart failure* 9 of 13 produced CRP It was stated that the CSR proved to be of practical value as complement to other diagnostic methods in revealing myocardial necrosis. The CSR is most certainly of service as CRP is always present in these cases and usually in high titer It was shown that it most often appears on the 2nd or 3rd day of disease reaches its maximum on the 4th, and then gradually decreases. A patient with an acute myocardial infarction is often admitted on the 2nd or 3rd day and at this juncture the determination of blood sugar and WBC is of less value as their maximum is reached during the 1st day of disease. From the very start when using the CSR in routine clinical work in 1942 it was evident that the appearance of CRP in the acute stage of myocardial infarction was of great value for diagnosis.

In six typical cases of subacute bacterial *endocarditis* the CRP titer remained at a medium high level for months with small transitory fluctuations in five. The negative patient had been successfully treated with penicillin.

Severe cases of *thrombosis* were shown to produce CRP and all patients with acute *pulmonary embolism*, 16, were also CSR positive. The appearance of CRP in cardiovascular diseases is further discussed in Chapter 7

Diseases of the digestive system 166 patients were examined. Only two of 88 patients with *peptic ulcer* reacted positively and no cases of *gastritis* 33 *ileus* 4 *melena*, 6, or *haematemesis* 6 showed CRP in the blood In later clinical surveys (65, 115, 125, 153) results in agreement with these have been found The appearance of CRP in patients with peptic ulcer are discussed in Chapter 9

Pregnancy No woman with a normal pregnancy 25 cases had a positive CSR and only one of 113 patients with varying degrees of toxaemia of pregnancy displayed a positive reaction. In 2 cases of intra uterine foetal death (5 cases examined) CRP appeared on the 4th and 5th day after cessation of the foetal heart beats.

Reports on the appearance of CRP during normal pregnancy are contradictory Some confirm the results in Paper II that a normal pregnancy does not influence the behaviour of CRP (11 31 65 125, 128, 141) Others found a relatively high percentage of CRP positive pregnancies (98 109 120 121 128, 140, 150) The discrepancy is difficult to explain. In all these surveys the CRPA technique was used except in Paper II (Löfström's CSR) and that of Muschel and Weatherwax (98) (complement fixation technique) Further studies on pregnancy sera using the CSR, CRPA and other methods on one and the same sera may perhaps explain the discrepancy

Infectious hepatitis 26 patients with acute infectious hepatitis were examined. Only three were positive and two of these were examined at an early stage of the disease Further investigations on infectious hepatitis have been performed and are presented in Chapter 8.

Tumours More than half of the patients with malignant tumours, 64 were CSR positive Cases with metastasis were usually positive It was pointed out that "it is not certain that metastasis in cancer brings about the formation of acute phase protein in the blood" One observation made by Löfström in 1943 was the positive CSR in patients with hypernephroma. All six cases of hypernephroma examined in Paper II had high-

titer CSRs. Many papers concerning CRP in malignancies confirm the findings in Paper II (22 46 110, 114 115 125 128, 132, 153)

Relation between CSR, erythrocyte sedimentation rate (SR) temperature white blood cell count (WBC) and blood smear The relationship between the appearance of CRP and various laboratory data was studied in cases of respiratory diseases, acute appendicitis myocardial infarction and diseases of the gall bladder (II)

Nearly every case of acute pneumonia had a SR above 12 mm/hour and temperature over 38 C in conjunction with the appearance of CRP Only half the pneumonia cases with a positive CSR, however had a WBC of more than 10,000 cells per ml

In acute appendicitis 60 % of the patients had a WBC of more than 10 000 per ml. It was concluded "that the determination of CRP is of still less help to the diagnosis of appendicitis than is a determination of white blood cells It was also stated that the CSR was of no practical value for the differential diagnosis of appendicitis.

Evidently the appearance of CRP and the elevation of temperature did not run a parallel course. 23 f 31 positive and 27 of 44 negative patients operated on for appendicitis had a febrile-subfebrile temperature. The same was also true for the cases with diseases of the gall-bladder

Concerning the relationship between CRP nd SR in the diseases under study t was stated that acute phase protein develops more quickly than does th enhancement of sedimentation rate. As a rule sedimentation rate remains considerably longer, than acute phase protein in acute conditions of disease" Anderson and McCarty (8) found in cases of rheumatic fever that the changes in the amount of C-protein present tend roughly to parallel changes in the erythrocyte sedimentation rate but this is by no means invariably true since C-reactive protein may be absent from the blood when the sedimentation rat is much higher than normal In many publications dealing with rheumatic disease the correlation between SR and CRP has been investigated (Hill 60, Lastman et al. 32, Rozansky et Davis 121)

Roantree and Rantz 1955 (115) made a comparison between temperature WBC and SR. They found that CRP gave fewer false positive reactions than the other indices of inflammation According to Yocum and Doerner 1957 (153) "CRP proved to be a more accurat test than the SR in the presence of inflammatory or necrotic processes" Dimmick (30) found the SR and CRP tests t be equally sensitive" and he stated th the SR was definitely more ... than the WBC" This is on the ... conformity w th the findings in P... in cases of pneumonia, acut ... respiratory diseases, operated cho... and in myocardial infarction as m... in Chapter 7 Among the 94 ... examined by Dimmick there ... cases of ppendicitis. Eastham and Davison (32) and Roz... Da is (121) ha e also treated subject w th similar results.

In Paper II it was stated formation of cute phase p... ngn either of infection or of of the body against degenera and that this organic rea... be registered through simp... measurement or sedimen... As th rise in temperature did not run parallel wit of CRP it was suggest

CRP estimation might be of good practical use when following the course of disease in cases of acute or chronic infection, cardiac infarction tumours, particularly hypernephroma, polyarthritis and in the control of non-specific excitation therapy Against the background of today's knowledge this statement still holds good.

After these early experiences of CRP in routine clinical work many questions still remained to be answered. The survey in Paper II indicated the possible use of this test as a diagnostic aid in the clinic. Since then, studies on CRP in different diseases, particularly cardiovascular diseases and disorders of the liver have continued The following chapters report on this work.

Occurrence of CRP in Myocardial Infarction and Cardiovascular Diseases

The results in the survey presented in Paper II indicated that the determination of CRP in cases of myocardial infarction was of particular value as a diagnostic test in routine clinical work. Investigations were therefore continued and a great many patients with cardiac diseases were studied. Particular interest was paid to CRP in myocardial infarction and congestive heart failure as *well as to the value of measuring the* CRP WBC, blood sugar and temperature for the diagnosis of myocardial infarction.

Material and methods

The study was conducted on a total of 235 patients hospitalized for myocardial infarction, 203 or congestive heart failure 32 during the years 1947—1955 in the IVth Medical Service of St Erik's Hospital in Stockholm. The diagnosis myocardial infarction was based on typical case history clinical course *ECG changes, blood sugar determination*, elevation of temperature and WBC. No selection of patients was made except that those suffering also from other diseases which might cause the appearance of CRP were excluded. Special attention was given the X ray *pictures of* the lungs — all patients showing signs of pneumonia being excluded. Sixteen patients had been treated for myocardial infarction twice and one patient had suffered attacks three times. Thus in all, 221 instances of myocardial infarction were examined

1st day of disease is the first 24 hours after onset of the attack, 2nd day the next 24 hours and so on.

Blood samples for CSR (described in Paper VII) WBC and blood sugar determinations were usually taken during the first morning in the hospital CSRs *and WBCs were then usually estimated* once a week or repeated when indicated. A WBC of over 10 000 cells/ml and a blood sugar over 120 mg were regarded as elevated.

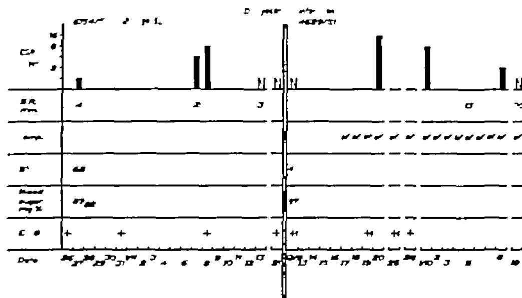
Temperature was measured in the morning and afternoon. Fever was regarded as a temperature of at least 38 C.

ECGs were taken every day or every second day during the acute stage, and later at least once a week. Standard polar extremity leads and unipolar chest leads CR_a IV R, J and CR 7 were used.

Autopsies were performed on 32 *patients who had died of myocardial infarction* and on 7 of cardiac insufficiency At autopsy the heart muscle was carefully examined and necrotic areas charted.

Table 8

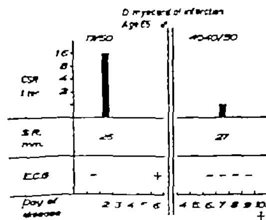
Number of patients	Number of myocardial infarctions	CRP	
		Positive	Negative
203	221	215	6



S.R. = sedimentation rate: n = normal temperature: sf = slight fever: Wbc = white blood count; N = negative.

Fig 11

The case in fig 11 (6154/50) represents patient who suffered twice from myocardial infarction. There is no exact information bout his first ttack. When admitted to the hospital, typical ECG changes had already developed. On the second day of hospitalization there was no increase in WBC or blood sugar During the whole course of the disease he had no fever nor elevation of SR. About twelve days after admittance his blood serum showed high CSR titer About a year later he was again admitted for myocardial infarction (4629/51) On the first day SR, blood sugar and WBC were normal. The ECG did not show significant changes on the 1st, 8th or 14th day after admission. At this time, his serum had a high CSR titer On the 17th day after admittance the ECG showed changes typical of myocardial infarction. The elevation of SR was slight.



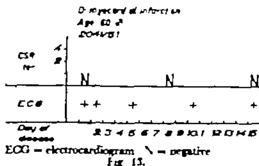
S.R. = sedimentation rate; ECG = electrocardiogram; N = negative.

Fig 12

The patient in fig 1 had also had two attacks of infarction. The first (case 17/50) showed no typical signs of coronary thrombosis. The diagnosis was later erified by ECG ECGs taken after the second onset which came several months later (case 4040/50) gav no clear information. Only one blood sample for CRP determination was taken on the 7th day of disease and low titer obtained. Autopsy showed typical old and fresh Infarctions.

2041/51 Fig 13 gives the clinical findings in case of myocardial infarction with negative CSR. ECGs indicated myocardial infarction and yet no CRP seemed to be present. The samples tested, however were drawn only on the 1st, 8th and 15th days.

4721/51 Six months earlier the patient had had an infarction, was admitted to the hospital and the diagnosis mistaken for another acute myocardial infarction. The ECG gave no clear evidence of fresh infarction but the CSR was positive after 8.



ECG = electrocardiogram N = negative
Fig 13.

It soon became clear that the cause of the positive CSR was symptomless maxillary sinusitis. As soon as the sinus was washed, the CSR became negative.

Results

Myocardial infarction

Of the 221 instances of myocardial infarction examined (Table 8) 215 showed at least one positive CSR during the acute course of disease

In six cases, CRP could not be demonstrated. These were tested as follows

No 4358/47 only once within the first 20 hours, No 7162/49 on the 1st and 8th day No. 2041/51 (fig 13) on the 1st, 8th and 15th day No. 5281/50 on the 2nd and 10th day No. 3546/52 on the 1st and 10th day of disease and No. 5059/49 only once 14 hours after onset of attack. The samples tested were in all six cases drawn either early when CRP might not yet have appeared in the blood or after the 8th or 10th day of disease by which time it might have disappeared. Even in these the CSR may have been positive.

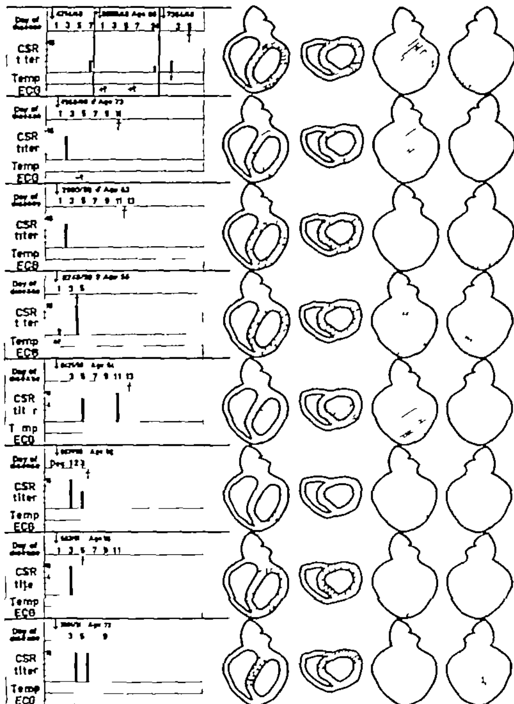
Of 215 cases clinically considered to be myocardial infarction and having a positive CSR, 177 showed ECG changes typical of heart infarction. In 37 cases it was not possible from the ECGs to decide if an infarction existed or not and in one case ECG was not taken, the diagnosis being revealed at autopsy (5054/53) Thus in 17 % of the cases examined ECGs could not give information about infarction.

The results can be further illustrated by some typical cases. Figs. 11—13

Autopsies CRP was shown in 30 of the 32 cases autopsied. Only in two was the CSR negative (nos 4358/47 and 5059/49) As already mentioned these patients were examined only once after 20 and 14 hours respectively Autopsy revealed that in two of the patients the necrotic heart muscle could not be regarded as the only cause of CRP production. One patient (6425/50) also suffered from emboli in different organs and one (1632/52) had fresh lung infarct and cerebral hemorrhage.

The ECGs showed signs of myocardial necrosis in 27 of the 32 cases autopsied. Thus in 16 % of the patients with a verified myocardial necrosis were the ECGs inconclusive. All five patients with atypical ECGs were CRP-positive

Schematic drawings of the old and fresh areas of infarction in the heart muscle of 15 patients are to be seen in figs 15 and 16 In these cases, myocardial infarction was the only source of CRP production. As seen, the extent of scars from earlier infarction and of fresh necrosis varies considerably from patient to patient. With regard to the individual



indicates onset of attack
afebrile
subfebrile
febrile
ECG electrocardiogram

fresh necrosis
scar tissue

Fig 14 The four drawings opposite each case represent the heart in longitudinal and transverse section and in front and rear profile.

variation It should be quite clear that it has not been poss ble to draw any definite conclus ons from the data in these figs as to the relationship between CRP prod ction and extent of necrosis

Congestive heart failure

Of 3? patients treated for cardiac insufficiency 18 were CSR-positive and 14 negative The degree of stasis varied both among the positive and negative cases but was no milder in the one group than in the other Most of the negative as well as the positi e patients had dyspnoea, cyanosis and peripheral oedema and X-ray revealed pulmonary stasis.

Five of the positi e and two of the negative patients died and were autopsied. In none of three pos tive cases was t possible to demonstrate any other source of CRP production than congesti e heart failure (5617/50 64?7/51 79/52) The negative patient had severe stasis with anasarca (3347/51)

Some examples may show the difficulties in determining the source of CRP in patients with congestive heart failure

2869/50 Age 61 Diagnosis: Cardiosclerosis nd fibrillation. During the first hospitaliza tion there was pulmonary stasis, severe oedema in the legs and palpable li er The blood was CRP-positive X-ray however re- vealed pneumonia. Seven months later he w again treated for severe cardiac insufficiency with th same severe stasis as on first admittance. This time no CRP could be demonstrated. About two years later he was again brought to the hospital with pains in the right side of the chest, blood in the phlegm and signs of cardiac insufficiency Several blood samples were CRP-positive. This time the cause was pulmonary embolism.

6580/50. Age 57 Diagnosis Essential hypertension, cardiosclerosis and cardiac insufficiency Myocardial infarction w th pul monary emboli six months before death. Severe heart insufficiency on last admittance. CSR titer 8 was shown in the blood nine days before death, SR 10 mm. Autopsy revealed acute and chronic stasis, parietal thrombus in the heart and an old renal infarct. I this case emboli may have been the source of CRP production.

6589/52. Age 67 Diagnosis Hypertension, cardiosclerosis and cardiac insufficiency Treat ed for cardiac insufficiency tw years pre iously The CSR was then negative. During his last admittance there were typical signs of congestive heart failure The CSR titer was 16 At autopsy old and fresh parietal

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4 14/48 Diagnosis Myocardial infarction. Three admissions. On the first occasion anterior infarction, on the second, symptoms of severe angina pectoris and on the third, severe myocardial infarction leading to death on 5th day Autopsy showed old and fresh infarction, small parietal thrombus in *the lef entricle Small area of encephalomalacia.*

4958/49 Diagnosis Myocardial infarction. Typical ttack with pains in the chest. ECGs gave no lear picture because of previous infarction. Autopsy showed old and fresh myocardial necrosis.

2900/50 Diagnosis Myocardial infarction and tertiary syphilis. Typical attack of infarction. Autopsy showed pericarditis in the region of the fresh necrosis. Parietal thrombus in the left ventricle.

6249/50 Diagnosis: Myocardial infarction Acut attack while isiting the surgical out patients department. Blood sample taken 17 hrs later was CRP-positive. Autopsy showed rupture in the wall of the left ventricle.

6425/50 Diagnosis Myocardial infarction. *Autopsy Parietal thrombus in the left* ventricle. Embolic infarct in lung and spleen. Cerebral malacia.

6821/50 Diagnosis Myocardial infarction and ulcus ventriculi. No pain. Autopsy One-week old infarct. Chronic ulcus ventriculi.

582/51 Diagnosis: Myocardial infarction. Autopsy Fresh infarct about one week old.

3894/51 Diagnosis Myocardial infarction. Autopsy Fresh infarct about 10 days old. Rupture of heart wall.

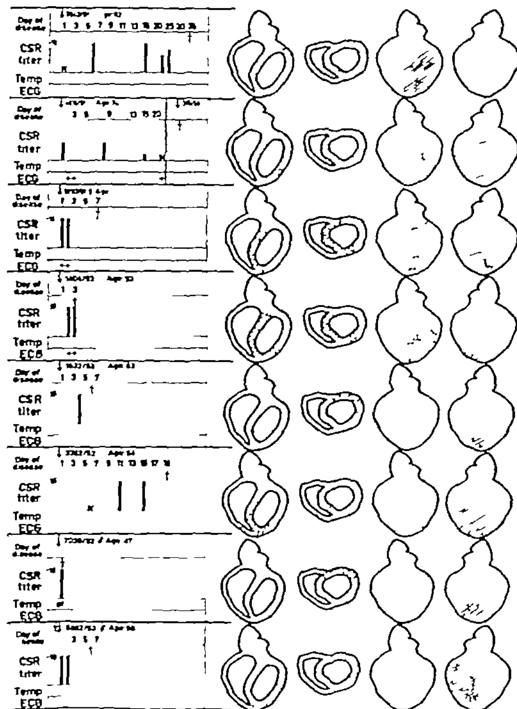


Fig. 15 The four drawings opposite each case represent the heart in longitudinal and transverse section and in front and rear profile.

thrombi i the left ventricle and embolic infarction in the lungs as well as in the kidneys were seen. The thrombo-embolic complication had not been revealed diagnostically.

As seen incompensation is very often accompanied by complications which can cause CRP production. In the three examples the complications were emboli with the formation of infarcts in lung and kidney and in two other cases cholecystitis could not be ruled out as the gall-bladders could not be seen on cholecystography. In three of the autopsied cases, however incompensation must be considered the only source of CRP production. It therefore seems as if congestive heart failure may of itself cause CRP production.

CSR, WBC, blood sugar and temperature.

On the 1st and 2nd day of myocardial infarction blood samples were tested concurrently for CRP WBC and blood sugar CRP and temperature were also estimated simultaneously The results are presented in Tables 9 10 and 11

In Table 9 it will be seen that on the 1st day of disease, 29 of the 42 patients tested showed a positive CSR while 22 had a WBC of over 10 000 Of the 24 patients tested on the 2nd day 23 showed a positive CSR and 13 had a WBC of more than 10,000

Table 9

Day of exami-nation	No. of patients ex amined	CSR		WBC cells/ml	
		pos.	neg	>10,000	<10,000
1st	42	29	13	22	20
2nd	24	23	1	13	11

On the 1st day (Table 10) 26 patients out of 41 had a positive CSR and in only 17 was the blood sugar level over 120 mg %

Table 10

Day of exami-nation	No. of patients ex amined	CSR		Blood sugar mg %	
		pos.	neg	> 120	< 120
1st	41	26	15	17	24
2nd	14	14	0	6	8

3942/51 Diagnosis Cardiosclerosis + myocardial infarction. Treated for myocardial infarction two years previously The attack began about 8 hours before first blood sample was drawn. This was CSR-negative.
4616/51 Diagnosis: Diabetes mellitus and myocardial infarction. The sample drawn about 10 hours after the first attack began. ECG on day of admittance showed signs of coronary insufficiency and myocardial damage. The ECG reading remained on the whole unchanged until the 8th day after admittance. Arhythmia present on day of admittance. The second attack two years later caused death.
5792/51 Diagnosis Hypertension, nephrosclerosis and myocardial infarction. Autopsy also showed pericarditis.
1404/52 Diagnosis Myocardial infarction. Autopsy revealed an 8—10 day old myomalacia and pericarditis.
1632/52 Diagnosis Hypertension, cardiosclerosis, pulmonary embolism and cerebral thrombosis.
3362/52 Diagnosis Myocardial infarction. The first blood sample taken on the 6th day was, surprisingly CSR-negative.
7039/52 Diagnosis: Myocardial infarction. The patient had suffered from angina pectoris for 5 years. Severe attack on day of admittance. Autopsy showed one-day old infarction.
5882/53 Diagnosis: Hypertension, congestive heart-failure myocardial infarction and arteriosclerosis. Patient treated several times in hospital for cardiosclerosis.

Table 11

Day of examination	No. of patients examined	CSR		Temperature	
		pos.	neg	> 38 C	< 38 C
1st	49	34	15	22	27
2nd	29	28	1	18	11

On the 1st day of disease, 34 of 49 patients examined were CRP positive and 22 had a temperature of at least 38° C (Table 11) Of 29 patients examined on the 2nd day 28 had a positive CSR and 18 a temperature above 38° C.

From the three Tables it is evident that both on the 1st and 2nd day after a myocardial infarction there were more patients with a positive CSR than a positive" WBC (more than 10 000 cells/ml) a "positive blood sugar test (more than 120 mg /) and a febrile temperature (more than 38° C) Thus CRP determination in a case of myocardial infarction is of greater diagnostic value than the determination of WBC, blood sugar or measurement of temperature.

Discussion

The CSR is a very sensitive, non-specific test. It is thus in the individual case often not clear what has induced the production of the reactive protein even in cases of clear clinical diagnosis. In the clinic t may be necessary to exclude several possible causes of CRP production before the real source is found. A sinusitis causing a positive CSR in a patient suspected of suffering from myocardial infarction may be the cause of an incorrect diagnosis as seen in case 4721/51

The clinical diagnosis of myocardial infarction is based not only on ECG findings but also on case history and laboratory tests. The ECG does not always give a definite picture even in cases of coronary thrombosis, not during the first days of disease anyway and it may be difficult to interpret, especially in patients where there has been earlier infarction In such cases a positive CSR may give information towards a correct diagnosis.

17 % of the patients with a clinical picture of myocardial infarction had no quite typical ECG changes, yet they did have a positive CSR. In these cases it was not possible to say with certainty that the patient had suffered from myocardial infarction ECGs did not give the final answer as shown by the autopsied cases. In five of the patients autopsied (16 %) ECGs did not reveal the infarct. All five had positive CSRs and at autopsy fresh infarctions were seen.

In the acute stage of coronary thrombosis the determinations of WBC, blood sugar and temperature are very often of value for diagnosis A WBC over 10,000/ml, an elevated blood sugar level of more than 120 mg / and a febrile temperature are often seen in acute myocardial infarction. The purpose of the comparison between CSR and WBC, and CSR and blood sugar level on the same blood samples was to find out which test was most valuable It was shown (Tables 9 and 10) that both on the 1st and 2nd day of disease there were more patients with positive CSRs than both positive" WBCs and blood sugar values. It was also evident that both during the 1st and 2nd day of disease more patients had a positive CSR than a temperature above 38° C (Table 11)

This study confirms the findings in Paper II where 47 of 48 cases examined showed CRP in the blood. It may thus be said that a real myocardial infarction with necrosis is followed by CRP production. This has been clearly demonstrated by the autopsied cases presented here. None of these had a negative CSR. Löfström's results (81) and the results in Paper II have also been confirmed by many authors (18 20 45 67 68 70 71 72 108, 114 115 125 153) Kroop and Shackman (68, 70 71) found the CRP test "sensitive and clinically helpful when the usual objective criteria for myocardial necrosis are equivocal or absent such as fever leukocytosis, elevated sedimentation rate and blood fibrinogen" Hedlund, in 1947 showed how the CRP SR, WBC, blood sugar tests and temperature behave in typical cases of myocardial infarction Paper II fig 8 and pointed out that CRP determination might be of more value than the determination of blood sugar and WBC for diagnosis. The comparison between CRP and WBC, blood sugar and temperature now presented confirm the results from 1947 The findings are also in agreement with those of Roantree and Rantz (115) whose 24 patients with recent myocardial infarct all had a positive CRP test while not all showed an abnormal SR WBC or temperature

14 of 32 patients with acute cardiac *insufficiency had no CRP in the blood* As complications which may cause the production of reactive substance are very frequent in congestive heart failure it is not possible from these results to state definitely that congestive heart failure does induce the production of CRP although it seems probable that it can, as three autopsied cases were found to have no other possible cause

The conclusion from this investigation and the general experience gained from many cases examined in the clinic is that CRP most commonly appears in the blood of patients with cardiac insufficiency This reactive substance, however usually originates from complications such as pneumonia, thrombosis, embolic infarction and myocardial infarction. Other causes might be asymptomatic cholecystitis and pyelonephritis.

Löfström in 1942 (80) and Hedlund in 1947 (II) reported positive CSRs in cases of congestive heart failure. One of Löfström's 8 cases and 9 of Hedlund's 13 showed positive CSRs. Similar findings have been made by others (27 31 34 49 115) Roantree and Rantz (115) supposed these positive reactions to be "due to complications of undiscovered thrombosis and embolism and that congestive failure itself does not result in the appearance of CRP" A similar opinion is expressed by Eastham, Szekely and Davison (31) and others (93 134) The most reliable means of verifying the source of CRP production is autopsy From the results of the three cases autopsied in this study it seems as if congestive heart failure may give rise to a positive CRP test.

To reach an understanding of a non-specific diagnostic test such as CRP determination in cardiovascular disease, it is of vital importance to carry out investigations *on patients suffering from only one* particular cardiac ailment and no other Many diseases difficult to reveal in the clinic in conjunction with a myocardial infarction may cause CRP production. The studies on the large number of autopsies presented are therefore specially intended to illustrate the relationship between acute myocardial infarction and the appearance of CRP

CHAPTER 8

Appearance of CRP in Diseases of the Liver

Since 1949 the CSR technique (Löfström's capsular swelling reaction) has been used as a routine test at the Hospital for Infectious Diseases in Stockholm on all cases of infectious hepatitis and other affections of the liver. Results of these tests are presented here. Special attention has been paid to the question if there is any difference between the duration of disease in a patient who is CSR positive during the acute stage and a patient who has no CRP in the blood during the whole course of disease.

Material and methods

In this study covering a period of three years (March 1953 to March 1956) three groups of patients are presented. During this time a ward of thirty beds was as a rule continually occupied, the number of patients one year amounting to about 300. Two thirds of the cases consisted of infectious hepatitis patients and the remainder had jaundice for other reasons.

One group — in the following marked O — consists of patients infected in Sweden by oysters kept in a sea water sump polluted by sewage. They were admitted to hospital during a relatively short period from the end of December 1955 to the middle of March 1956. The total number of oyster patients treated was about 250. For reasons explained below, the number of patients studied was reduced to 224 (90 female and 134 or 59.8 % male).

The second group — in the following marked X — consisted of hepatitis patients infected either in Sweden or abroad and studied during the period in question. During the three-year period the investigation was in progress, the total number of X hepatitis patients amounted to about 600. Only 183 of these, however, are included in the study. The X material was composed of 84 females and 99 males (54.1 %). The most important difference between the O and X materials is of epidemiological nature. The O group has a uniform epidemiological origin while the X group is composed of cases which most often had no epidemiological connection with each other. The O group is entirely composed of cases of infectious hepatitis whereas group X includes 9 cases which most probably suffered from serum hepatitis.

The reduction in the number of patients in both O and X groups was made for different reasons. Hepatitis patients who were suffering from other diseases such as pneumonia, sinusitis, urinary infections etc. which might also cause CRP production were excluded from the study. Many cases had to be left out as they remained in hospital for too short a time. As the duration of disease was

always calculated from "1st day of disease" (see below) only patients with a clear onset were included in the study. Some patients never showed an "abnormal" value for the tests in question and therefore could not be used for certain parts of the study. The great reduction in the X group is mainly because the author who performed the CRP test himself, was on leave of absence from the hospital for long periods during the investigation in question and only cases examined both by the author and by a specially trained technician are included. The exclusion of cases was always a matter of chance.

The third group consisted of patients having jaundice for reasons other than *hepatitis*. In all these cases the diagnosis was verified at autopsy or in the operating theatre except for some with cirrhosis of the liver.

Each hepatitis patient was examined as follows: on admittance the laboratory liver tests seen below were performed and the blood examined for the presence of CRP. All tests were repeated once a week.

Blood samples for examination were drawn in the morning by venipuncture before the patient had eaten. CSR (CRP test) — described in Paper VII.

Bilirubin in the serum was quantitatively estimated according to Jendrassik and Grof (62). A "normal" value was taken as a bilirubin level which had sunk to at least 1.8 mg %.

Bromsulphalein excretion test according to Rosenthal and White (118). A value of less than 6 % in the serum 45 mins after an intravenous injection of 5 mg bromsulphalein per kg body weight was taken as a "normal" value.

Galactose tolerance test according to Bauer (13). A "normal" level was taken as an excretion of 3 g or less in the urine within six hours after an intake of 40 g by mouth.

Thymol turbidity test performed according to MacLagan (84). A "normal" reaction was taken as 6 units or under in the serum.

The patients were usually treated in the hospital until they gave a "normal" bromsulphalein reaction — not tested for until the bilirubin level had reached "normal". The galactose test was made in conjunction with the bromsulphalein. After discharge from hospital the patients were controlled in the outpatient department about one month later and then at intervals of one to three months.

For the calculations it was necessary to know the recovery time for each patient. As it is difficult to determine this strictly the most practical method of investigation seemed to be to record the time it took for each patient to attain a "normal" calculable value for each laboratory test used. This "recovery time" was calculated from the "1st day of disease" which denotes the point of time when the first symptoms of the preicteric stage appeared. In most of the cases, this prodromal stage was characterized by subjective symptoms such as anorexia, malaise, fatigue, headache, nausea, vomiting, chilly sensations and arthralgia. The patients arrived in the hospital at different stages of disease, as a rule one or two days after the appearance of jaundice.

Results

Hepatitis

Of the 224 cases in group O 122 or 54 % were CSR positive. Of these 122, 40 were females (33 %). The 102 negative cases included 50 females (49 %). There

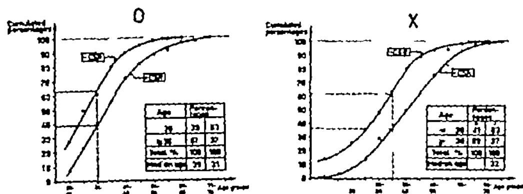


Fig. 16. Age distribution of CRP-positive and negative O and X patients. Observations made on 122 positive and 102 negative O patients and on 94 positive and 89 negative X patients.

were about the same proportion of positive cases in group X — 94 of 183 i. e. 51 %. Of these 94, 42 were females (45 %). Of the 89 negative cases, 42 were females (47 %).

CRP could as a rule be shown in the preicteric and the icteric stage on admittance and then for a varying period, in some patients for only a few days, in others up to several weeks. The results are to be seen in Table 12. Of the O patients, 65 % became CRP negative within 3 weeks whereas the corresponding figure for the X patients is 39 %, a difference which is highly significant statistically.

Most of the patients showed a low titer, the values varying between 1 and 32. The highest titer value reached by each patient is recorded in Table 13.

The relationship between CRP and age is to be seen in fig. 16 where the cumulated percentages of CSR-positive and negative patients are plotted against various age groups. It is to be seen that the majority of the O patients were adults.

The two curves refer to O patients who were CRP positive and those who were CRP-negative the whole time. The curves indicate that the positive patients have an average age higher than the negative. The median age of positive patients is roughly 8 years greater than that of the negative. By following the dotted lines, it will be seen that 39 % of the positive patients are under 36 years of age, the corresponding figure for the negative is 63 %. In the inset table, the material is divided into two age groups, less than 36 and greater than or equal to 36 years. It will be seen that for the positive patients there are more in the older age group (61 %) than in the

Table 12. Duration of CRP positivity

Patient material	Number of patients with positive CSRs for weeks									
	1	2	3	4	5	6	7	8	9	10
O	13	32	34	10	7	8	2	0	4	12
X	5	21	12	20	9	11	8	2	2	4

Table 13. Titers obtained

Patient material	Number of patients with a CSR-titer of					
	1	2	4	8	16	32
O	39	35	30	8	9	1
X	26	25	28	15	1	1

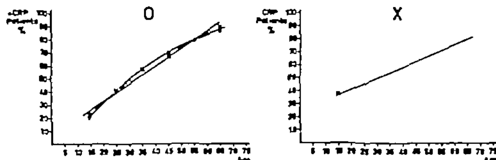


Fig 17 Percentages of O and X patients in different age groups showing positive CSRs. The diagrams are calculated on total of 224 O patients, 122 of which had positive CSRs, and on total of 183 X patients, 94 of which had positive CSRs.

= observed values, ● = calculated values.

younger (39) For the negative patients the situation is reversed (37 and 63)

A similar tendency is seen for X patients. Here there exists the same mutual relationship between the curves as between the curves for the O patients i. e. that CRP-positive patients are of a higher average age. The median age of the positive cases is about 9 years greater than that of the negative.

Calculations according to the t test indicate that there is a highly significant difference between the mean ages of the positive and negative patients in both the O (t = 5 46 t 222 degrees of freedom) and the X group (t = 5 41 at 181 degrees of freedom)

The connection between age and appearance of CRP is further illustrated in the diagram presented in fig 17 The O and X materials were divided into 10-year age groups 1—10 11—20 etc. For approximation the means of these groups, 5 15 etc. have been used and in the fig these plotted against the respective number of CSR positive patients expressed in percentages of the whole material. By means of the method of least squares, a straight-line graph and curve of the second degree were adapted to the O values, and a straight line graph only to the X values. The points obtained in the X diagram are not so regularly situated as those in the O diagram.

From the diagram in fig 17 O it will be seen that the curve is better adapted to the recorded values than the straight line. The difference between the two functions is almost negligible in the region covered by observed values and hardly of any importance for the estimation of the frequency of positive and negative cases in different age groups. There were few observations in the end-groups and so they have been left out of the diagram. In the year-group 1—10 there were 5 O patients, all negative, and 14 X patients, 13 negative and one positive (10 years old) In the age group 66—70 there were 4 positive O patients and 2 positive and one negative X patient. The graphs in figs 16 and 17 indicate that positive CRP tests are more often seen among the older patients than among the younger i. e. there is a greater risk for older patients to become CRP positive.

The relationship between the recovery time" estimated for each of the laboratory

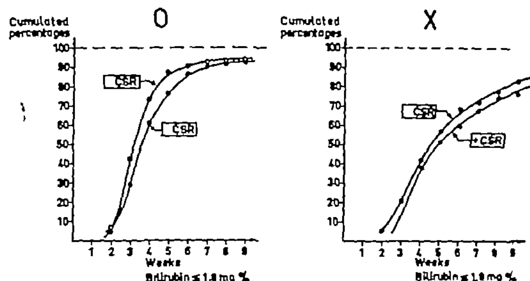


Fig 18. Recovery time" for the bilirubin test in O and X patients with positiv and negative CSRs. Observations made on 98 positiv and 83 negativ O patients, and on 87 positiv and 83 negative X patients.

tests and the results of the CRP deter minations is illustrated graphically in a number of curves. It was thus calculated how many CSR positive and CSR negative patients reached normal' test values within different periods of time — recorded in weeks for the bilirubin (fig 18) bromsulphalein (fig 19) and galactose tests (fig 20) and in months for the thymol test (fig 21) The results have been plotted as cumulated per centages of case material on the vertical axes against recovery time" on the horizontal The points were fairly regular ly situated and it has thus been possible to draw satisfactory freehand curves from them.

It was not always possible to obta n all final normal test values for each patient, consequently the number of cases quoted in the results is less than the total number possible. This loss of material was, however insignificant ex cept for galactose where the curves had to be based on a relatively small number of observations for this reason. The curves do not reach the 100 % limit because the last time-interval classes are open-ended. It is thus unknown where the last point along the time axis should be situated.

The curves in the following figs 18—21 indicate what part of the whole group shows a normal test value at a certain point of time after the onset of disease.

Fig 18 shows that the positive and negative curves for the O and X patients are separate almost throughout the whole range, the negative lying above the positive indicating that on the average it takes longer for the CSR positive patients to attain normal" *bilirubin* values.

In fig 19 both O and X curves lie well apart, indicating that it takes longer for the positive patients to reach normal" *bromsulphalein values* For half the O ma



Fig. 1[illegible]. Recovery time for the bromsulphalein test in O and X patients with positive and negative CSRs. Observations made on 1[illegible] positive and 5[illegible] negative O patients, and on [illegible]3 positive and 84 negative X patients.

terial the median time takes 4 weeks for the negative and more than 5 weeks for the positive. Corresponding figures for the X material are over 4 weeks for the negative and over 6 for the positive.

Similar curves for the galactose test in fig. 20 also indicate that it takes longer for the CSR positive cases in both O and X groups to attain "normal" values.

The results of the thymol turbidity test plotted in fig. 21 show an analogous picture; here the time has been calculated in months and not weeks.

Both O and X materials thus seem to behave in the same way — it takes longer for CSR positive patients to attain "normal" test values than for negative.

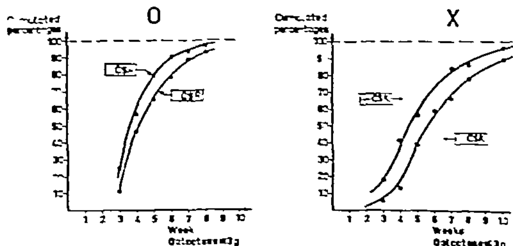


Fig. 20. Recovery time for the galactose test in O and X patients with positive and negative CSRs. Observations made on 83 positive and 70 negative O patients, and on 59 positive and 50 negative X patients.

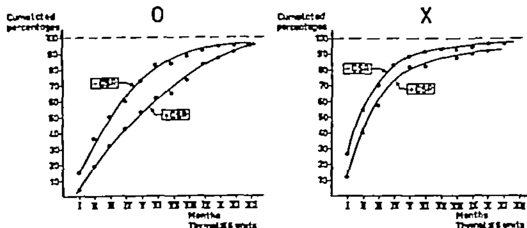


Fig. 21 "Recovery time" for the thymol test in O and X patients with positive and negative CSRs. Observations made on 118 positive and 86 negative O patients, and on 60 positive and 53 negative X patients.

In figs 18—21 the influence of the age factor was not taken into consideration. An investigation was therefore made to see if the difference in "recovery time" between CSR-positive and negative cases could also be shown in different age groups. Results are presented in Table 14 a. With regard to the distribution in the materials, both O and X patients were divided into two age groups, one up to 36 years and the other 36 years and over. What part of the two age groups recovered within a certain time was investigated. This "recovery time" was fixed as a period of four weeks for the bilirubin, bromsulphalein and galactose tests, and four months for the thymol test, these periods being chosen with respect to the length of time it took for about half the patients to reach "normal" values. Only the number of patients who had reached "normal" values for the different tests were recorded (total number of patients tested given in italics). These figures are expressed as percentages in order to make it possible to compare results from the + CSR group with those from the — CSR group.

It will be seen that a greater percentage of negative O patients less than 36 years of age (66 %) attained a "normal" bilirubin value (below 1.8/mg %) within 4 weeks than the equivalent age group in the positive patients (50 %). A similar relationship is found in the older age group, 68 % among the negative and 50 % among the positive.

The same type of relationship as in the bilirubin examination is evident for the O patient *bromsulphalein* test i. e. that a higher percentage among the negative patients in the younger age group (49 %) attained "normal" reaction within 4 weeks than among the positive in the same age group (30 %). There is a similar relationship between the older age groups, 37 % negative against 22 % positive.

The O material displays the same tendency — higher negative figures — in the *galactose* test for the younger age group (55 % against 36 %). In the older

Table 14 a. Showing the relationship between "normalizing" of laboratory tests made on CSR-positive and negative patients under and over 36 years of age. ("Normal" values reached within 4 weeks — thymol within 4 months). The percentages refer to the number of cases included in each respective test (figures in italics). The total numbers of patients are given in italics at the bottom of the table.

Tests	O patients				X patients			
	< 36 years		≥ 36 years		< 36 years		≥ 36 years	
	+ CSR	— CSR	+ CSR	— CSR	+ CSR	— CSR	+ CSR	— CSR
Bilirubin ≤ 1.8 mg	*45* 50	*5* 66	*66* 30	*39* 68	*35* 42	*7* 43	*33* 19	*29* 28
Bromsulphalein ≤ 6	*47* 30	*37* 49	22	*33* 37	*38* 18	*48* 33	*49* 6	*30* 27
Galactose ≤ 3 g	*3* 36	*31* 35	*61* 39	*30* 40	*38* 14	*2* 40*	*6* 10*	*39* 20*
Thymol ≤ 6 units	*45* 50	*62* 73	*70* 37	*34* 50	*79* 76	*39* 80*	*41* 59	*18* 72
The whole material		*64*	*74*	*38*	*39*	*36*	*55*	*33*

Table 14 b. Calculated χ^2 values at comparison between the + CSR and — CSR values in Table 14 a.

	O patients		X patients	
	< 36 years	≥ 36 years	< 36 years	≥ 36 years
	+ CSR — CSR	+ CSR — CSR	+ CSR — CSR	+ CSR — CSR
Bilirubin	2.721	2.536	0.000	0.752
Bromsulphalein	4.000	2.800	3.744	6.55.
Galactose	5.411	0.004	5.488	1.67*
Thymol	5.900	1.560	0.127	1.002

χ^2 values at different levels of significance

10	2.71
5	3.84
2	5.41
1	6.64

group, however, the figures are almost equal.

The tendency is also evident in the *thymol* test — a higher percentage among the negative O patients in the younger age group.

Turning to the X material, the tendency towards higher percentage figures among the CSR-negative patients than among the positive in both age groups for the galactose, bromsulphalein and thymol tests is found. The younger age group in the bilirubin test, however, shows no difference (43 against 42 %) although the older age group is in conformity (28 negative against 19 positive).

For all tests investigated here there is thus a tendency that a relatively larger number of both O and X patients in the CSR-negative group attain "normal" test values within four weeks, for the thymol test within four months.

Using the χ^2 test, a comparison between CSR + and — values from Table 14 a was made and the result is to be seen in Table 14 b. A level of 5 % (3,84)

Table 15

Diagnosis	Number of cases CSR	
	+	−
Cholecystitis		
Cholelithiasis	30	11
Carcinoma of the pancreas	35	0
Carcinoma of the liver and biliary ducts.	22	0
Cirrhosis of the liver	31	3

was taken as of applicable significance. It will be seen that no significant difference between CSR-positive and negative cases can be shown in either the X or the O bilirubin test. A significant difference was, however found for the younger O and older X bromsulphalein, younger X galactose and younger O thymol groups. Two points are to be noticed in the table, that bromsulphalein values for all groups show fairly large differences throughout and that the younger O patients also show fairly large differences for all tests.

Jaundice from causes other than hepatitis

The results of CRP determination in patients suffering from jaundice of non-hepatitis origin are presented in Table 15

It will be noticed here that the cholecystitis and the cholelithiasis cases are mainly positive. These ailments are presented together as it is often difficult to differentiate them in the clinic. Among the 11 negative cases there were 5 with pure cholelithiasis without inflammation and 6 showing chronic cholecystitis changes without signs of acute inflammation All patients with a verified carcinoma were CSR positive.

With three exceptions, patients with cirrhosis of the liver showed a positive CSR during hospitalization. All the negative patients showed a typical clinical picture of cirrhosis of the liver with positive laboratory tests. One of these was a 10-year old boy (700/56) with a severe progressive chronic hepatitis. He was kept under observation for several years. Biopsy revealed pronounced portal cirrhosis. The two other patients showing no CRP production were females. One 48 years of age (2323/55) had a severe progressive disease and one 34 years old (67/52) died from an acute extensive necrosis of the liver

Discussion

In the survey made in 1947 Paper II CRP was demonstrated in 3 out of 26 cases of acute infectious hepatitis. Several papers dealing with the appearance of CRP in hepatitis have been published since then (43 50 65 115 125 143 146 153) Havens, Eichman and Knowlton (50) were unsuccessful in showing the presence of CRP in 90 cases of this disease. This might possibly depend upon the degree of sensitivity of the C-polysaccharide test used by them. Wood and McCarty in 1951 (146) showed that this test was not sensitive enough to show the appearance of CRP in cases of acute infectious hepatitis. Both Löfström's CSR (Paper II and Paper VII) and the CRPA technique described by Wood and Mc Carty (146) have, however shown themselves to be sensitive enough. Hedlund, Paper VII made a comparative study on the sensitivity of the CRPA and CSR methods. Among the 592 sera used, 318 were from cases of infectious hepatitis and the two methods were shown to have an equal sensitivity When using the CRPA technique, Roantree and Rantz (115) Selman and Halpern

(125) and Vest and Marti (143) could show the appearance of CRP in cases of acute infectious hepatitis while Yocum and Doerner (153) had negative results for all 18 cases in estigated by them.

In the present work, CRP was found in about 50 of the hepatitis material both in cases of an isolated ep demic (O-group) and in cases of isolated infection (Y-group) The CRP appeared mostly during the preicteric and icteric stages of disease Those cases in which it appeared for longer period usually had a severe d sease of long duration.

Some authors ha e noted that hepatitis often affects the older more severely than the younger (7 15, 17 78 94 122) In a Danish epidemic it was found that such type of disease occurred more often in women over 45 years of age (7 17) Mannbeck Stockholm 1956 (94) noted that the severity of the icteric phase rose successively w th age. During the study presented here, the clinical course of the illness was not found to be more severe after the menopause. It was shown however that there is a greater risk for older patients to become CRP-positive

A significant difference was shown to exist between the mean age of the positive and negati e patients in both O and Y groups. It was also found that there is a greater risk for the positive patients to suffer from a longer course of disease, the duration being measured by the time t takes for liver test values to attain normal" values.

The period of four weeks for recovery time" was chosen rather arbitrarily The course of the curves, however indicates that the results would have been mainly the same if another "recovery time had been chosen for the calculations.

From the results in Table 14 b t was found that the largest differences occurred in the bromsulphalein test. This is of interest as it was considered to be the most reliable method of liver function measurement of the tests used Significant differences were not found to exist between positive and negative CSR patients in some of the groups. However it should be noted that the same tendency towards longer recovery time" for CSR positive patients was demonstrated in two different materials with four different tests.

The O-group material seems to be of special value for study as t may be assumed that there was a single source of infection and furthermore all patients were treated during the relatively short period of two months. This decreases the possibility of variation in laboratory test technique perhaps influencing results from th Y material which was examined over a period of several years. In any case, the conformity between O and Y materials is remarkably good as regards the appearance of CRP although t should be noted that far more O than Y patients became CRP negative after 3 weeks (Table 12)

The detection of CRP may be of diagnostic aid in diseases of th liver and biliary ducts. As seen in Table 15 CRP is generally found in such diseases. In cases of infectious hepatitis the titers seldom reach high levels and usually disappear soon, while in malignancies of the pancreas and biliary ducts and in cholecystitis the titers are often constant and of a high value. In cases of cholelithiasis proper CRP is as a rule absent as evident from the five negative cases and the material presented in Paper II (52) A positive CSR in a patient with a typical attack of cholelithiasis is thus a good indication that the gall bladder is inflamed.

The experiences reported in this study confirm the results won in 1947 Paper II It may be observed, however that the malignancies treated in the hospital had most often reached an advanced stage of disease. In the early stages of carcinoma of the biliary ducts and even of the pancreas, the CSR some times fails. In spite of the limitations of this test, however the determination of CRP may be of value for differential diagnosis when used in malignancies.

The results of the CRP test in cirrhosis of the liver (Table 15) may be misleading The predominance of positive cases may depend upon the fact that the cirrhotic patients treated in the hospital are in the acute stage of disease. The sensitivity of the liver for toxic products during convalescence was revealed during this study by the fact that patients in the recovery stage of cirrhosis when the special liver tests were approaching "normal" values were found to give a positive CSR after the intake of alcohol Another observation worth noting was made during this study In the most severe case of liver necrosis there was no production of CRP and in severe cirrhosis of the liver which progressed for months there was no positive CSR during the whole course of disease although there was clear evidence of liver damage

No conclusions as to the possible importance of CRP determination for estimating the prognosis of infectious hepatitis can be drawn from the data presented The possible importance of CSR titer values and the duration of CRP in the blood for the course and prognosis of disease have not been investigated. Further studies on this material may perhaps give an answer to these questions.

Summary

C-reactive protein (CRP) or acute phase protein was studied both from experimental and clinical points of view. The purpose of the experimental studies was to investigate the sensitivity of the method used for the determination of CRP, which animal species beyond those already known could produce it and in which ways this substance may be produced in humans and animals. The properties of CRP were studied in electrophoretic and absorption experiments. The primary goal of the clinical work was to chart the pathological conditions in which CRP appears and to discover of what help this might be for the diagnosis.

Experimental studies

The two methods hitherto most often used for determining CRP are the non-specific capsular swelling reaction (CSR) and the specific CRP antiserum method (CRPA). It was shown that both had the same value as regards sensitivity. It was concluded that the CRPA method *is easier to use for those unfamiliar with microscopy*, whereas the CSR was superior in that it better permits the determination of quantitative differences.

Hitherto acute phase protein has been found in man, monkey and rabbit. In experiments performed on mice, hens and guinea pigs, it was shown that these animals are also capable of producing it. Sera from all these species were found to *induce non-specific capsular swelling* of pneumococci types 11 A, 23 B and 27. It was also shown that baby rabbits only a few hours old are able to produce the substance.

Different ways of inducing acute phase protein in man and animals are accounted for and in the first experiments agents thought to be effective in non-specific stimulation therapy were tested. Injections of manganese, gold and copper salts, sulphur and sterile milk were found to induce acute phase protein production in rabbits, while injections of Omnadin and autoblood were not found to. Man became CSR positive after injections of manganese salt, sulphur and typhoid vaccine. Most of the animals reacted promptly on stimulation. Some, however, failed to react, indicating individual reaction to the stimulation. Animals treated over a long period with a constant, large dose of manganese salt or sulphur showed decreasing CSR titers. A similar tendency was also found in humans.

Typhoid vaccine was shown to be a more reliable rabbit stimulating agent than sulphur. Repeated injections of the vaccine brought about lower CSR titers than the first injection. This tendency was more marked after stimulation with sulphur. Living bacteria induced a high acute phase protein titer in the animals, but for experimental

*work this agent was considered un*suitable.

CRP appears in humans in response to non-infectious stimuli such as resorption of necrotic tissue as in myocardial infarction. Attempts were made to induce CRP production experimentally in an analogous way. Tissues from the same species as well as breakdown products of proteins such as peptones and amino acids were therefore studied for their ability to induce acute phase protein production in rabbits. It was found that injections of various rabbit organs (heart, lung liver kidney muscle, spleen, lymph gland) ground and suspended in sterile pyrogen-free saline as well as injections of a mixture of blood from several rabbits stimulated production. This was achieved after subcutaneous, intramuscular and intraperitoneal site of injection. A large number of the animals also gave a positive CSR after injections of pepsin-digested suspensions. Necrotic tissue brought about by frostbite skin lesions was shown to induce production in rabbits. Peptones as well as a solution of amino acids used for the intravenous nutrition of humans were found capable of inducing CxRP production while pyrogen free saline was not.

Most often elevation of temperature and appearance of CRP run a parallel course. Experiments were therefore performed on rabbits and humans to investigate whether an elevation of temperature in itself might induce production. Rabbits were artificially heated in an incubator (37 C) for 6½ hours. Patients treated for chronic luetic diseases were examined for their ability to produce CRP when subjected to a temperature of about 40 C for 2—3 hours in an ultrapandorus apparatus. Seven of eight *rabbits reacted with positive CSRs. All* blood samples from the patients were negative.

Artificial elevation of temperature was also induced by intravenous drip of a suspension of formalin-killed bacteria. CRP could be demonstrated in humans after a fever period of 10—20 hours, the maximum titer appearing 18—22 hours after the beginning of administration. The correlation between the appearance of CRP and the rise in white blood cell count and sedimentation rate was studied. The findings of these tests were similar to those found in cases of myocardial infarction. Sodium salicylate medication was shown to exert no influence on the production of CRP.

In these experiments there were many opportunities of studying the appearance time of acute phase protein. The shortest in the rabbits was found to be 6 hours. This was recorded after the animal had been heated in an incubator for 6½ hours. The appearance time was usually 16—18 hours after the different sorts of stimulation. After administration of vaccine to humans, it appeared at the earliest after about 12 hours. The shortest time found in the clinic was 8 hours in a patient with myocardial necrosis.

Experiments were further performed to obtain information about the composition of CRP by electrophoresis and cross-absorption and about its presence in leukocytes, lymphocytes and lymph.

With the aid of continuous zone electrophoresis, the CRP was found to migrate with the gamma-globulins. The validity of the results was checked by analytical electrophoresis tests in free solution and on filter paper. The C-reactive substance was tested for by Löfström's CSR method and also with the CRPA method for comparison. Discrepancies in the

results of various electrophoretic experiments published by different authors were discussed

As absorption agents in the cross-absorption experiments, suspensions of pneumococci types 1 23 B and 27 a suspension of hemolytic streptococci type 1 Dochez C-reactive protein antiserum C-polysaccharides of type 1 23 B and 27 and bovine albumin were used From the results it was concluded that the CRP in human serum consists of at least two components.

Acute phase protein could not be obtained from rabbit lymph and lymphocytes or from human leukocytes.

Clinical studies

By means of the CSR, the sera of some 2 000 patients with a wide variety of diseases were investigated for CRP activity Charting of the diseases as to CRP production gave a rough picture of those in which the CSR could be of differential diagnostic value. Special interest was devoted to the value of the CSR as a diagnostic aid in acute appendicitis, diseases of the biliary ducts and rheumatic and cardiovascular diseases. The relationship between the CSR and various laboratory data (sedimentation rate, temperature white blood count and blood sugar) was studied in cases of respiratory disease, acute appendicitis, diseases of the gall bladder and myocardial infarction.

CRP was demonstrated in every instance where elevated temperature was associated with inflammation. The active protein, however was also found in relative abundance without any accompanying rise in temperature. CRP was shown to develop more quickly than a rise in sedimentation rate In acute conditions, the sedimentation rate remained elevated considerably longer than the C-reactive protein was present No parallel was found to exist between white blood count and presence of acute phase protein The CRP pattern differed in cases of rheumatic fever and rheumatoid arthritis. In the latter the protein was most often found to a moderate degree in the active stage of disease and as the patient improved the protein did not disappear as in cases of rheumatic fever but persisted for a long time in low concentration.

The investigations on the use of CRP determination in cardiovascular disease published in 1947 were extended 203 patients with myocardial infarction and 32 cases of congestive heart failure were studied. In 221 instances of myocardial infarction CRP was demonstrated in 215 The correlation between the appearance of CRP and ECG findings were discussed and illustrated by drawings from 16 autopsied cases.

It was shown that both on the 1st and 2nd day after a myocardial infarction more patients had a positive CSR than an abnormal white blood count, blood sugar or febrile temperature.

Incompensation is very often accompanied by complications which can cause CRP production. It is thus difficult to discover what really causes a positive CSR in congestive heart failure. In three cases the only source of CRP production seemed to be the congestion as no other source could be found at autopsy

In a study on about 400 patients suffering from infectious hepatitis, CRP was found in more than 50 both in cases of isolated epidemic and of isolated infection. The CRP appeared mostly during the preicteric and icteric stages of

disease. Those patients in whom it appeared for longer periods usually suffered from a severe form of the disease for a long time. It was shown that there was a greater risk for the older to become CRP positive than for the younger and that this indicated a more prolonged course. The duration was measured by the time it took for liver test values to return to calculable "norms".

In malignancies of the pancreas and biliary ducts and in cholecystitis the CRP titers were often constant and of a high value. In cases of cholelithiasis proper CRP was as a rule absent.

CRP could most often be demonstrated in the blood of patients in the acute stage of cirrhosis of the liver. It was not possible, however, to demonstrate CRP in some patients with severe progressive cirrhosis of the liver although there was clear evidence of liver damage.

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References

1. AARONSON A L, KAPLAN M A, GOLDIN A, LIBERTI, A and GOLDIN B. Ann. Allergy 13, 586 1955. C-reactive protein in bronchial asthmatic patients further evaluation.

2. ABERNETHY T J and FRANCIS T J Exp Med. 65 59 1937 Studies on the somatic C-polysaccharide of pneumococcus. I Cutaneous and serological reactions in pneumonia

3. ABERNETHY T J J Exp Med. 65 75 1937 Studies on the somatic C-polysaccharide of pneumococcus. II The precipitation reaction in animals with experimentally induced pneumococcic infection

4. ABERNETHY T J and AVERY O T J Exp. Med. 73 173, 1941 The occurrence during acute infections of protein not normally present in the blood; I Distribution of the reactive protein in patients sera and the effect of calcium on the flocculation reaction with C-polysaccharide of pneumococcus.

5. ADAMS, F H. J A M A 156. 1319 1954 Newer concepts in diagnosis and treatment of rheumatic fever

6. ADAMS, F H. J Pedia 49 16 1956. Appraisal of certain acute phase reactants in single blood sample and their value in the diagnosis of acute rheumatic fever

7. ALFIERI, G Am. J Med. Sciences. 213 257 1947 Studies on malignant hepatitis.

8. ANDERSON, H C. and McCARTY M. Am. J Med. 8 445, 1950 Determination of C-reactive protein in the blood as measure of the activity of the disease process in acute rheumatic fever

9. ANDERSON, H. C. and McCARTY M J Exp. Med. 93 25 1951 Occurrence in the rabbit of an acute phase protein analogous to human C-reactive protein

10. ASH, R. J Inf. Dis. 53 89 1933 Non-specific precipitins for pneumococcic fraction C in acute infections.

11. B[illegible] A and STENDERUP A Ugeskrift for læger 122 671 1960. C-reaktivt protein under gra[illegible]idi[illegible]et [illegible]ed fodslen og puerperiet.

12. B[illegible], H and SEITZ, D Klin. Wchschr 31 323, 1953 Klinische Untersuchungen uber das Aku Phase Protein (C-reaktives Protein)

13. B[illegible], R. Med. Klin. 22 1558 1926. Zur Frage des Icterus catarrhalis.

14. BELLOMO, G and MUSCOLINO, F Lattante 30 264 1959. La proteina C reattiva nel sangue funicolare ed in alcune condizioni fisiopatologiche del neonato.

15. BERGSTRAND, H. Georg Thieme Verlag, Leipzig 1930. Über die akut und chronische gelbe Leberatrophie

16. BINO, J Acta path. 23. 540, 1946. Histological changes after intraperitoneal injection of proteins and protein-hydrolysates.

17. BJORNEBOE, M., JERSILD, M., LUNDBAEK, K. HIM THA[illegible] E. and RYSSING, E. Lancet I 867 1948 Incidence of chronic hepatit in women in Copenhagen, 1944—45.

18. BJORNEBJO, K. B.: S Läkartidn. 56 3675, 1959 Om bestämning av C-reaktivt protein serum.

19. BJORNEBJO, K. B WEBER, I and ODEN, L. Scand. J Clin. Lab. Invest. 11 238 1959. The influence of surgery on serum and urine hexosamine serum mucoprotein, glutamic-oxaloacetic transaminase (GOT) and C-reactive protein.

20. BO[illegible]AN, A. J and FISCHEL, E. E Am. J Med. 20 418 1956. Serologic tests for inflammation serum complement, C-reactive protein and erythrocyte sedimentation rate in myocardial infarction.

21. BRATTSTEN I Arkiv Kemi 8 205, 227 347 1955 Continuous zone electrophoresis by crossed velocity fields in supporting medium.

22. BRENNAN, M. J GOODMAN M and SHIPMAN, W L. Proc Am. Assoc. Cancer Res. 2 96, 1956. Orosomucoid, C-reactive protein and albumin variances measured immunochemically in cancer patients. II Clinical correlation.

23 Bunim, J J Kuttner, A. G., Baldwin, J S. and McEwen, C. J A. M. A. *150* 1273, 1952 Cortisone and corticotropin in rheumatic fever and juvenile rheumatoid arthritis.

24. Bunim, J J Pechet M. M and Bollet A. J: J A. M. A. *157* 311 1955. Studies on metacortandralone and metacortandracin in rheumatoid arthritis.

25. Bustamante, Victor: Bulletin de la Société de Chimie Biologique 39 155, 1957 Étude immuno-électrophorétique sur papier et gélose de la localisation des différents anticorps bactériens et la Crp.

26. Bustamante, V Arino, J and Preud, L. M. Presse Méd., Paris *65*. 315, 1957 Localisation de la protéine C-reactive dans les fractions electrophoretiques du serum.

27 Bywaters, E. G. L. Circulation *14* 1153 1956. Treatment of rheumatic fever

28. Carlens, E. Acta oto-laryng 29 316, 1941 Serological studies of acute otitis with particular regard to non-specific capsular swelling of type 27 pneumococci.

29 Carlson F S and ...: Acta rheum. scand. *1* 267 1956. The diagnostic significance of acute phase protein in synovial exudates.

30. Dorrock, B. M.: Am. J Med. Technol. 23, 53, 1957. A report of C-reactive protein.

31 Eastham, R. D Szekely P and Davison, K.: Annals Rheumat. Diseases *17* 314 1958. C-reactive protein in rheumatic heart disease.

32. Eastham, R. D Szekely P and Davison, K. Annals Rheumat. Diseases *17* 319 1958. Comparison of the erythrocyte sedimentation rate, C-reactive protein, serum diphenylamine, and tetrammonium tests in rheumatic fever and rheumatic heart disease.

33. Elster, S. K., Wood H. F and Seely R. D Am. J Med. *17* 826, 1954 Clinical and laboratory manifestations of postcommissurotomy syndrome

34 Elster, S. K., Braunwald, E. and Wood, H F Am. Heart. J *51* 533 1956. Study of C-reactive protein in the serum of patients with congestive heart failure.

35. Elster, S. K. and Wood, H F J Clin. Invest. 33 931 1954. Studies of the C-reactive protein in the Post-Commissurotomy" syndrome.

36 Elster, S. K. and Wood, H. F Am. Heart J *50* 706, 1955 Studies of C-reactive protein in patients with rheumatic heart disease lack of correlation between C-reactive protein and Aschoff bodies in left auricular appendage biopsies.

37 Finland M. and Dowling, H. F J Immunol. 29 283 1935. Cutaneous reactions and antibody response to intracutaneous injections of pneumococcus polysaccharides.

38. Fischel, C. W Vaughan, N A. and Rothbart M. V J Inf. Dis. *106* 174 1960. Serologic and fractionation studies of C-reactive protein.

39. Fischer, F Stendeerup A., Bangsgaard-Andersen, T och Clemmensen, T Ugeskrift for Laeger *120:* 303, 1958 C-reaktivt protein, Kliniske undersøgelser

40. Francis, T and Abernethy T J J Clin. Invest. *13* 692, 1934. Cutaneous reactions in pneumonia to the somatic ("C") polysaccharide of pneumococcus.

41 Fukuda, M., Henckell, Ch. L. and Carpenter, Ch. M.: Am. J of Clin. Pathology 32: 507 1959 A method for quantitative determination of C-reactive protein using gel-diffusion.

42. Gál, K. and Miltényi, M. Acta Microbiol. Acad. Scient. Hungaricae 3 41 1955 Haemagglutination test for the demonstration of C-reactive protein.

43. G utier, A. and Veit M.: Ann. Pædiat. *186* 210, 1956. Zur Bestimmung des C-reaktiven Proteins bei verschiedenen Erkrankungen im Kindesalter

44. Gautier, A. and Scheitlin, J J: Schweitz Med. Wschr *87* 950, 1957 Qu est-ce que la Protéine-C.

45. Goldner, F and Meador, C. South. Med. J *48.* 1539 1955. Transaminase and C-reactive protein levels in acut myocardial infarction evaluation of indices of necrosis.

46. Goodman, M., Bridgman M. J and Simpson, W L. Proc. Am. Assoc. Cancer Res. 2. 111 1956. Orosomucoid, C-reactive protein and albumin variances measured immunochemically in cancer patients. I Methodology

47 Halbert S. P Swick, L. and Sonn C. J Exp. Med. *101* 557 1955 The use of precipitin analysis in agar for the study of human streptococcal infections. II Ouchterlony and Oakley technics.

48. Hamer, A., Marner, I. L. and Egby Poulsen, P Scand. J Clin. Lab. Invest. *11* 37 1959 The acute phase protein reaction C-reactive protein.

49. Harris, T N Friedman, S. and Tang, J

Am. J. M. Science 234 259 1957 Paradoxical values of the erythrocyte sedimentation rate in rheumatic fever A comparison among three acute phase tests.
50. HAVENS, W. P. JR., EICHM H. L. and KNOWLTON M. Proc. Soc. Exp. Biol. 5 108, 1950. Failure to find C-reactive protein in infectious hepatitis.
51. HEDLUND, P. Acta med. scand. 118 529 1944 The production of the acute phase protein after nonspecific stimulation.
52. HEDLUND P. Acta med. scand. Suppl. 196 579 1947 The appearance of acute phase protein in various diseases.
53. HEDLUND, P. Nord. Med. 35 461 1947 Bacteriologic and serologic findings in rheumatic fever in the light of the clinical picture
54. HEDLUND, P. FRISK, A. R. and BUCHT H. Acta med. scand. 131 417 1948. The appearance of acute phase protein after induced fever in man.
55. HEDLUND P. and BRATTSTEN, I. Scand. J Clin. Lab. Invest. 7 99 1955 Electrophoretic analysis of human acute phase protein.
56. HEDLUND, P. FRISK, A. R. and BUCHT H. Scand. J Clin. Lab. Invest. 8 207 1956. The effect of salicylic acid medication on the formation of acute phase protein in the blood.
57. HEDLUND, P. and BRATTSTEN, I. Scand. J Clin. Lab. Invest. 8. 213, 1956. Isolation of acute phase protein by means of continuous zone electrophoresis.
58. HEDLUND, P. Scand. J Clin. Lab. Invest. 9 218, 1957 A Comparison between the Löfström capsular swelling reaction and the CRPA-method (C-reactive protein antiserum) for determination of acute phase protein in human serum.
59. HILL, A. G. S. Lancet 2 807 1951 C-reactive protein in chronic rheumatic diseases.
60. HILL, A. G. S. Lancet 2: 558, 1952. C-reactive protein in rheumatic fever
61. HOKAMA, Y. COLEMAN, M. K. and RILEY R. F. J Immunology 85. 72, 1960. C-reactive protein response in rabbits during immunization with foreign proteins.
62. JENDRASSIK, L. and GROF P. Biochemische Zeitschrift 297 81 1938. Vereinfachte photometrische Methoden zur Bestimmung des Blutbilirubins.
63. KAPLAN, M. A., AARONSON A. L., HENDERSON, J. and GOLDIN M. Ann. Allergy 13 29 1955. C-reactive protein levels and antistreptolysin O titres in bronchial asthma.
64. KELLEY V. C. GOOD, R. A. and McQUARRIE I. Pediatrics 5 824 1950. Serum mucoproteins in children in health and disease with special reference to rheumatic fever
65. KNIGHTS, E. M. J. HUTCHINS, M. MONO V E. and PLOOMPUU J. J. A. M. A. 162. 9 1956. Use of C-reactive protein test as screening procedure for blood donors.
66. KNIGHTS, E. M. and HUTCHINS, M. Bibliotheca haematolog Fasc. 413, 1958. Evaluation of the C-reactive protein test as screening procedure for blood donors.
67. KOZONIS, M. C. and GURFVITY I. Ann. Int. Med. 46 79 1957 The value of the C-reactive protein determination in coronary artery disease
68. KROOP I. G. and SCHACKMAN, N. H. Proc. Soc. Exper Biol. & Med. 86 95, 1954 Level of C-reactive protein as measure of acute myocardial infarction.
69. KROOP I. G. and SCHACKMAN N. H. Clin. Res. Proc. 3 119 1955. The effect of surgical trauma and the rheumatic state on C-reactive protein formation.
70. KROOP I. G., WEIDEN, P. and SCHACKMAN, N. H. Circulation 12 735, 1955. The C-reactive protein determination as diagnostic aid in the coronary disease
71. KROOP I. G. and SCHACKMAN, N. H. Am. J. Med. 22. 90, 1957 The C-reactive protein determination as an index of myocardial necrosis in coronary artery disease.
72. LEVINSON, E. L., LEVY H. and ELSTER, S. K. Am. Int. Med. 46. 68 1957 Study of C-reactive protein in the sera of patients with acute myocardial infarction.
73. LEWIS, A. J. PADER, E. & ELSTER, S. K. Am. J. Med. Sc. 233. 309 1957 The effect of salicylates and adrenocortical hormones on C-reactive protein.
74. LIBRETTI, A., KAPLAN, M. A. and GOLDIN, M. Proc. Soc. Exp. Biol. 90 481, 1955. Precipitin analysis of C-reactive protein by gel diffusion.
75. LIBRETTI, A. and KAPLAN, M. A. J. Allergy 27 450, 1956. Role of C-reactive protein in allergic inflammation; relationship between acute phase response and antibody titer
76. LIBRETTI, A., GOLDIN, M. and KAPLAN, M. A. J. Immunol., Baltimore 79 306, 1957

Immunologic relationship of C-reactive protein from various human pathologic conditions.

77. Loewer, S. and Volk, B. W. N. Y. J. Med. *56* 2665, 1956. Newer laboratory procedures indicating rheumatic activity.

78. Lucké, B. and Mallory, T. Am. J. Path. *22* 867, 1946. The fulminant form of epidemic hepatitis.

79. Löfström, G. Nord. med. *2* 1927, 1939. Serologic studies in acute pneumonias.

80. Löfström, G. Acta med. scand. *110* 49, 1942. Nonspecific capsular swelling in pneumococci.

81. Löfström, G. Acta med. scand. *141* 57, 1943. Nonspecific capsular swelling in pneumococci.

82. Löfström, G. Brit. J. Exper. Path. *25* 21, 1944. Comparison between the reactions of acute phase serum with pneumococcus C-polysaccharide and with pneumococcus type 27.

83. Löfström, G. Acta med. Scandinav. Suppl. *196* 575, 1947. Acute phase serum in rabbits: capacity of pneumococcus strains which react specifically with type 16 anti-pneumococcus serum to cause nonspecific capsular swelling with acute phase serum from rabbits.

84. MacLagan, N. F. Brit. J. Exper. Path. *25* 234, 1944. Thymol turbidity test; new indicator of liver dysfunction.

85. MacLeod, C. M. and Avery, O. T. J. Exp. Med. *73* 183, 1941. The occurrence during acute infections of a protein not normally present in the blood. II. Isolation and properties of the reactive protein.

86. MacLeod, C. M. and Avery, O. T. J. Exp. Med. *73* 191, 1941. The occurrence during acute infections of a protein not normally present in the blood. III. Immunological properties of the C-reactive protein and its differentiation from normal blood proteins.

87. McCarty, M. J. Exp. Med. *85* 491, 1947. The occurrence during acute infections of a pro   not normally present in the blood. IV. Crystallization of the C-reactive protein.

88. McCarty, M. Ann. I   Med. *37* 1027, 1   Present status of diagnostic tests for rheuma   er.

89. McCarty, M. Triangle (The Sandoz J. of Med. Science) *4* 142, 1960. The C-reactive pro   n.

90. McEwen, C., Bunim, J. J., Baldwin, J. S., Kuttner, A. G., Bass, Appel, S. and Koltman, A. J. Bull. New York Acad. Med. *26* 212, 1950. The effect of cortisone and ACTH on rheumatic fever.

91. McEwen, C. Am. J. Med. *17* 794, 1954. The treatment of rheumatic fever.

92. McEwen, C. Med. Clin. North America *39* 353, 1955. Recent advances in diagnosis and treatment of rheumatic fever.

93. McEwen, C. and Ziff, M. Med. Clin. North America *39* 763, 1955. Basic sciences in relation to rheumatic diseases.

94. Mansbeck, Hj. Acta Med. Scand. *155* 353, 1956. The course of infectious hepatitis of varying ages and its spread among different social groups.

95. Marner, I. L. and Hansen, A. Scand. J. Clin. Lab. Invest. *11* 44, 1959. The acute phase protein reaction. II. Clinical application.

96. Mitchell, J. J. Laborat. M. Soc. *107* 68, 1955. Diagnosis of rheumatic fever.

97. Montella, S. and Wood, H. F. J. Exp. Med. *106* 321, 1957. Studies on the Cx-reactive protein. II. Inhibition of the C-reactive protein response in rabbits by blockade of the reticulo-endothelial system.

98. Mitchell, L. H. and Weatherwax, R. J. Proc. Soc. Exp. Biol. *87* 191, 1954. Complement fixation in the C-reactive protein system.

99. Müller, W. Zeitschr. für Rheumaforschung *15* 31, 1956. Über die Bedeutung des C-reaktiven Proteins bei der Beurteilung der Aktivität akuter rheumatischer Erkrankungen.

100. Müller, W. and Kahler, H. J. Deutsche med. Wchnschr. *81* 1410, 1956. Das Auftreten des C-reaktiven Proteins im Serum verglichen mit der Blutsenkung, dem Serumkupfer und Eisenspiegel, verschiedenen Serumlabilitätsreaktionen und dem weissen Blutbild.

101. Müller, W., Klein, N., Matthes, M. Zeitschrift für Rheumaforschung *17* 226, 1958. Die Präzipitationsanalyse des C-reaktiven Proteins im Agar-diffusionstest und seine Lokalisation in der Immunelektroforese.

102. Nevin, R. L., Roberts, P. H. and LeDeaux, S. B. J. Ped. S. Louis *51* 493, 1957. Observations of antistreptolysin-O, C-re-

active protein and electrophoretic protein patterns in maternal and neonatal sera.

103 NAKAMURA, K. J Kyoto, 65 1193 1959 Gel diffusion and immunoelectrophoretic studies of C-reactive protein with particular reference to its presence in hemoglobin SS disease

104 NORDBRING F and PHILIPSON L Acta Paediat. 48 53, 1959 C-reactive protein in human colostrum.

105 OTTAVIANI, A Arch. Italiano di otol. rinolaringol 0 157 1959 La proteina C nel siero nel secreto nasale in alcune affezioni delle vie aeree superiori. Ricerche sierologiche ed immunoelettroforetiche

106. OUCHTERLONY O Acta Path. Microbiol. Scand. 25 186, 1948. In vitro method for testing the toxin producing capacity of diphtheria bacteria.

107 PERLMANN E. BULLOWA, J G M and GOODKIND, R. J Exp. Med. 77 97 1943 An immunological and electrophoretic comparison of the antibody to C-polysaccharide and C-reactive protein of acute phase serum.

108 PHEAR, D & STIRLAND, R. Lancet 273 270 1957 The value of estimating fibrinogen and C-reactive protein levels in myocardial ischaemia.

109 PHILIPSON L. and TIITERÄS, E. Acta Pediatr 46. 1 1957 C-reactive protein in infancy Its appearance during the first year of life transplacental passage and electrophoretic pattern.

110. PIRILA, V and SALO O Acta derm ven. 39 17 1959. The occurrence of CRP in skin diseases

111 RAHMAN, S. and MOZZICONACCI, P La Semaine des Hôpitaux de Paris. 33. 1 1957 La C. réactive protéine dans le rhumatisme articulaire aigu.

112. RAPPORT M. M. and GRAF L. Proc. Soc. Exp. Biol. 93 69 1956. Quantitative determination of C-reactive protein by complement fixation.

113 RAPPORT M. M., SCHWARTZ, A. E. and GRAF L. Ann. Surg 145. 321 1957 C-reactive protein in patients following operation.

114 ROANTREE, R. J and RANTZ, L. A. Clin. Res. Proc. 3. 63, 1955. The clinical significance of the measurement of serum C-reactive protein.

115. ROANTREE, R. J and RANTZ, L. A. A. M. A. Arch. Int Med 96 674 1955. Clinical experience with C-reactive protein test.

116 ROANTREE R J PETERSON, F A. and RANTZ, L A. Clin Res. Proc 5 150 1957 The identification of the C-reactive protein and various antibodies in the serum gamma globulin obtained by continuous flow paper electrophoresis.

117 ROBERTS, E. M Clin North America 38 1 03 1954 Rheumatic fever and active rheumatic heart disease

118 ROSENTHAL, S M and WHITE, E. C. J A M. A 84 1112 1925. Clinical application of the bromsulphalein test for hepatic function.

119 ROTHBARD, S., WATSON R. F SWIFT H F and WILSON, A. T Arch. Int Med. 6 229 1948. Bacteriologic and immunologic studies on patients with hemolytic streptococcic infections as related to rheumatic fever

120 ROZANSKY R. and BERCOVICI, B. Proc Soc Exp. Biol. Med. 92 4 1956. C-reactive protein during pregnancy and in cord blood.

121 ROZANSKY R., D m, E. Am. J Clin. Path. 29 331 1958. Relation between C-reactive protein and erythrocyte sedimentation rate in rheumatic fever

122. SAYERS E. G Med. J Australia 11 613 1952. Infectious hepatitis in older age groups.

123. SALO, O TUOMIOJA, M. Ann. Med. Exp Biol. Fenn. 36 223, 1958. Cross-reactivity of the factors involved in the APC and CRP tests.

124 SCHULTZE, H. E., SCHWICK, G., SONNET J HEREMANS, J MICHAUX, J L. Klin. Wschr 38. 62, 1960. Gamma A-Globulin, eine immunoelektrophoretisch nachweisbare γ-Globulin Komponente mit Beziehungen zum C-reaktiven Protein.

125 SEEMAN, D and HALPERN, A. Angiology 7 292, 1956. Pitfalls in the determination of C-reactive protein, an acute-phase reactant.

126. SHACKMAN N H HEFFER, E. T and KROOP I G. Am. Heart J 48. 599 1954 C-reactive protein determination as measure of rheumatic activity

127 SHETLAR, M. R., PAYNE, R. W STRENGE, H. B. and FAULKNER, J B. J Pediatr 51 510, 1957 Objective evaluation of patients with rheumatic diseases. III. Comparison of serum glycoprotein, seromucoid, and

C-reactive protein determinations as methods for the evaluation of patients with rheumatic fever
128. SHETLAR, M. R., BULLOCK, J. A., SHETLAR, C. L. and PAYNE, R. W. Proc. Soc. Exp. Biol. Med. *88*: 107 1955 Comparison of serum C-reactive protein, glycoprotein and seromucoid in cancer arthritis, tuberculosis and pregnancy
129. SHUBIN, H., GLASKIN, A. and HEIKEN, C. A. Tuberculology *15*. 62, 1955. Value of *CRPA (C-reactive protein agent) compared* to blood sedimentation studies in tuberculosis.
130. SINGER, J. M., PLOTZ, C. M., Pader E. and ELSTER, S. K. Amer J Clin. Path. *28*. 611 1957 The latex fixation test. III Agglutination test for C-reactive protein and comparison with the capillary precipitin method.
131 SMITH, J M. and SKAGGS J T J Allergy *27* 338, 1956. C-reactive protein in allergic diseases.
132. SPRUNT D H. and HALE, W M. Proc. Amer Am. Cancer Res. 2. 47 1955. A method of evaluating cancer tests.
133. STEIN, E. and SMITH, J M. A. M. A. J Dis. Child. *91* 150, 1956. C-reactive protein in the acute phase of common contagious diseases.
134. STOLLERMAN, G H., GLICK, S., PATEL, D J HIRSCHFELD, I. and RUSOFF J H. Am. J. Med. *15* 645, 1953. Determination of C-reactive protein in serum as guide to the treatment and management of rheumatic fever
135. STOLLERMAN, G H., GLICK, S. J and ANDERSON, H. C. Proc. Soc. Exp. Biol. *87* 241 1954. Effect of adrenocortical hormones on presence of C-reactive protein in blood.
136. SVENSSON, H. and BRATTSTEN, I. Arkiv Kemi *1* 401 1949 An apparatus for continuous electrophoretic separation in flowing liquids.
137 TIDWELL, R. A. and LEWIS, D. Northwest Med. *55* 777 1956. C-reactive protein, its uses and limitations in the practice of pediatrics.
138. TILLETT W S. and FRANCIS, T JR. J Exp. Med. 52. 561 1930. Serological reactions in pneumonia with non-protein somatic fraction of pneumococcus.
139. TUFT H. S and SCHERR, M. S. J Allergy *27* 344 1956. Significance of C-reactive protein in asthmatic patients.
140. TYLER, C. W and ROHR, T J Amer J Obstetr Gynec. *73*. 837 1957 C-reactive protein in pregnancy
141 VALENTINI, A. and FOGLI, C. Minerva Ginecologica *10*. 984 1958. Proteina C reattiva stato gravidico-puerperale sangue fetale.
142. VOLTERRI, A., SLOAN J M. and BARNESS, L. A. Pediatrics *25*. 106, 1960. C-reactive *protein in serum in nephrosis and* acut glomerulonephritis.
143. VEIT M. and MARTI, J Schweiz. Med. Wschr *87* 782, 1957 Über das Auftreten von C-reaktivem Protein und dessen Verhältnis zu Senkungsreaktion, Weltmann-Band und Electrophorese bei verschiedenen Krankheiten im Kindesalter
144. WADSWORTH, C.: Internat. Arch. Allergy *10*: 355 1957 A slide microtechnique for the analysis of immune precipitates in gel.
145. WAHLÉN Tore.: Acta Tuberc. Scand. *26* 58, 1952. Passive transfer of tuberculin hypersensitivity by viable lymphocytes from the thoracic duct.
146. WOOD, H. F and MCCARTY M. J Clin. Invest. *30*: 616, 1951 The measurement of C-reactive protein in human sera. Comparison of the clinical tests on the basis of quantitative method.
147 WOOD, H. F J Exp. Med. *98*. 311 1953. The relationship between the acute phase response and antibody production in the rabbit. I. Correlation between the early appearance of Cx-reactive protein and subsequent antibody production.
148. WOOD, H. F J Exp. Med. *98*: 321 1953. The relationship between the acute phase response and antibody production in the rabbit. II. The stimulation of Cx-reactive protein response by certain adjuvants and the relation of this response to the enhancement of antibody formation.
149 WOOD, H. F MCCARTY M. and SLATER, R. J J Exp. Med. *100*. 71, 1954. The occurrence during acute infections of protein not normally present in the blood. V Physical-chemical properties of the C-reactive protein crystallized by a modified technique.

150. Wood, H. F. and McCarty, M. Am. J. Med. 17: 68, 1954. Laboratory aids in diagnosis of rheumatic fever and in evaluation of disease activity.

151. Wood, H. F. and Mosteller, S. J. Exp. Med. 10? 315, 195? Studies on the Cx-reactive protein. I. The effect of administration of Cx-reactive protein to normal rabbits.

152. Yaffee, H. A. M. A. Arch. Derma. 75: 696, 1957. The C-reactive protein in diseases of the skin.

153. Yocum, R. S. and Doerner, A. A. A. M. A. Arch. Int. Med. 99: 74, 1957. A clinical evaluation of the C-reactive protein test.

154. Ziegra, S. R. and Kuttner, A. G. Am. J. Med. Sciences 516, 1951. Reappearance of abnormal laboratory findings in rheumatic patients following withdrawal of ACTH or cortisone.

155. Zinnemann, K. J. Klin. Wochenschrift 37: 160, 1959. Zur Lokalisation des C-reaktiven Proteins im Eiweisspektrum des Serums.

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SUPPLEMENTUM 302

ON THE PROGNOSIS AND NATURAL HISTORY OF ACUTE RHEUMATIC FEVER AND RHEUMATIC HEART DISEASE

BY

PAUL HALL

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SUPPLEMENTUM 362

FROM THE DEPARTMENT OF MEDICINE, MALMÖ GENERAL HOSPITAL, MALMÖ
UNIVERSITY OF LUND
DIRECTOR: PROFESSOR J. WALDENSTRÖM

ON THE PROGNOSIS AND NATURAL HISTORY OF ACUTE RHEUMATIC FEVER AND RHEUMATIC HEART DISEASE

A STUDY BASED UPON A 25-YEAR MATERIAL IN A SWEDISH TOWN SERVED BY A SINGLE HOSPITAL

BY

PAUL HALL

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ABBREVIATIONS

A.H.A. = American Heart Association
N.Y.H.A. = New York Heart Association
A.R.F = Acute rheumatic fever
R.H D = Rheumatic heart disease
M.S. = *Mitral stenosis*
M.I. = Mitral incompetence
M.S M.I. = Mitral stenosis with incompetence
A.S. = Aortic stenosis
A.I. = Aortic incompetence
A.S.A.I. = Aortic stenosis with incompetence
ECG = Electrocardiography
P C.V = Pulmonary capillary venous pressure
E.S.R. = Erythrocyte sedimentation rate
AST = Antistreptolysin titre

PREFACE

This investigation was suggested by my former chief and teacher Professor C Biörck under whose guidance it was started. Without his encouragement and generous support I should never have ventured int this field of research.

Sincere thanks go to my chief Professor J Waldenström f r constructive criticism and timulation as well as for placing laboratory facilities at my disposal.

I thank Professor H Wulff for kindly allowing me to publish cases operated upon for mitral stenosis as well as for fruitful discussions.

I am much bliged to Professor S. Winblad for kind interest and for valuable suggestions as well as for the pathologic anatomic material from the years 1944—55

For all roentgen examinations acknowledgement is due to Professor S. Welin.

T the heads of the departments of medici e infectious diseases, orthopaedics, and paediatrics — Professor J Waldenström, Doctor H H llst n Docent S. von Rosen and Docto P Selander I am indebted for willing co-operation.

Invaluable help with the statistical analysis of the data was given by Docent G Blom.

I wish to express my thanks to Mrs Terttu Nilsson Miss Karin Sonesson and Mrs Yvo ne le Veau fo technical assistance

Thanks go to the Board of the Malmö General Hospital for providing technical assistance with the analysis f the material and particularly to Mr E. Tenshult and Mr O Nantin for kind help with the punch card system

To all persons and institutions colleagues and collaborators t the heart laboratory I feel grateful.

The investigation was supported by grants from Malmö stad Svenska Livförsäkringsbolags förening, Kung Gustav V:s 80 års fond Riksföreningen mot Reumatism and from the Medical Faculty f the University in Lund.

Malmö February 4 1961

Paul Hall

INTRODUCTION

The literature on acute rheumatic fever and rheumatic heart disease is voluminous and n merous studies on large series have been published but none f these investig tions were made in one population. Malmö is ne of the few t wns in the world that is really suitable for epidemiological investigations, because the town has only ne hospital and that hospital caters for a population of more than 200,000 inhabitants. This advantage was theref re utilized to study the natural history and th prognosis of acute rheumatic f ver and rh umatic heart disease

The hospital records and parish registers were studied for the subsequent course of cases of acute rheumatic fever and rheumatic heart disease admitted to Malmö General Hospital in 1930—54 and representative groups f the survivors were reviewed in 1953 or later The data obtained were analyzed in the hope that it would contribute to our knowledge of the natural history of the disease

DEFINITIONS

ACUTE RHEUMATIC FEVER

According to the criteria accepted by American Heart Association (A.H.A.) and given below acute rheumatic fever (A.R.F.) is related to a previous infection with beta hemolytic streptococci but the underlying mechanism is not known. As yet, there are no specific diagnostic laboratory tests.

In 1944 JONES divided the diagnostic features of the disease into major and minor categories according to their relative occurrence in rheumatic fever In 1955 these criteria were modified by the A.H.A. They are designed only to guide the clinician towards a diagnosis of the disease and to distinguish this disease from others and to restrict the diagnosis of rheumatic fever to illnesses with accept able criteria. General acceptance of these criteria would also permit comparison of series collected in different parts of the world.

According to the A.H.A., these criteria are only of diagnostic significance being of no significance as to prognosis degree of rheumatic activity or severity of acute illness.

MAJOR CRITERIA

CARDITIS

Carditis as evidenced by one or more of the following changes:

Murmurs

(a) A significant apical systolic murmur apical mid-diastolic murmur o basal diastolic murmur in an individual without a history of previous rheumatic fever or in whom there is no reason to assume pre-existing rheumatic heart disease. (b) A change in the character of any of these murmurs during observation of an individual with rheumatic fever (c) Roentgenologically manifest advancing cardia enlargement.

MAJOR CRITERIA	MINOR CRITERIA
Carditis	Fever
	Arthralgia
Polyarthritis	Prolonged P—R interval in the ECG
Chorea	Increased E.S.R. or presence of C-reactive prot in, or leukocytosis
Subcutaneous nodules	Preceding beta hemolytic streptococcal infection
Erythema marginatum	Previous rheumatic fever or inactive rheumatic heart disease

Pericarditis

Pericarditis manifested by a friction rub pericardial effusion or definite electrocardiographic evidence

Congestive failure

Congestive failure (in a child or young adult under 25) in the absence of other manifest causes.

POLYARTHRITIS

Polyarthritis tends to be migratory and is manifested by pain and limitation of active motion or by tenderness heat redness or swelling of two or more joints. Arthralgia alone without objective evidence of joint involvement is not a major manifestation

CHOREA

This must be differentiated from habit spasm, athetosis, and cerebellar ataxia Movements must be characteristic involuntary and of moderate severity if chorea is to be used as a major manifestation

SUBCUTANEOUS NODULES

These are shot-like hard bodies seen or felt over the extensor side of certain joints, particularly elbows, knees and wrists in the occipital region or over the spinous processes of the thoracic and lumbar vertebrae

ERYTHEMA MARGINATUM

This recurrent pink characteristic rash of rheumatic fever in which the colour gradually fades away from its sharp scalloped edge is found mainly over the trunk, sometimes on the extremities but not on the face It is transient — is brought ut by heat and migrates from place to place

MINOR CRITERIA

FEVER

A significant rise in temperature is a common symptom but as t occurs in so many illnesses, it has little differential *diagnostic value In order to be included* the elevation of temperature must clearly exceed the normal diurnal fluctuation, which may vary widely from individual to individual.

ARTHRALGIA

Pain clearly located without objective findings is only a minor criterion for diagnosis. The pain must be in the joint not in the muscles or other periarticular tissues, and it must be distinguished from the nocturnal pain in the extremities occurring in normal children Arthralgia must not be used as a minor criterion when polyarthritis is included as a major one

PROLONGED P-R INTERVAL IN THE ELECTROCARDIOGRAM

Prolongation of the P R interval may be non specific; it is considered a minor criterion and is not diagnostic of carditis. It cannot be used if carditis is already included as a major manifestation.

INCREASED ERYTHROCYTE SEDIMENTATION RATE, PRESENCE OF C-REACTIVE PROTEIN, OR LEUKOCYTOSIS

One or more of these non specific signs may be considered as a single criterion. Particularly to be deplored is the tendency to use any of these tests as a major criterion or as diagnostic of rheumatic fever

EVIDENCE OF PRECEDING BETA HEMOLYTIC STREPTOCOCCAL INFECTION

This must be documented by a history of scarlet fever or by a typical clinical picture of another streptococcal infection preceding the onset of rheumatic fever by one week to one month the nature of the infection being confirmed by a history of immediate contact with other individuals having typical streptococcal infection or by positive culture of material from the nose or throat in which beta hemolytic streptococcus predominates, or by an elevated or rising antistreptolysin-O titre

PREVIOUS HISTORY OF RHEUMATIC FEVER OR THE PRESENCE OF INACTIVE RHEUMATIC HEART DISEASE

The existence of either of these may be used as a minor criterion in deciding the rheumatic nature of the illness in question but only if the previous history can be documented by the same objective criteria as are set forth in this statement r by the presence of inactive rheumatic heart disease

According to the cr teria set up by the Ameri can H art Association the presence of two major criteria or one major and two minor criteri ind ates a high probabil ty f the presence of rheumati fever

COMMENTS

In order to secure uniform criteria for the present material which dates back t 1930 it was f und necessary to modify the criteria of the A.H.A. in a few respects.

The conception of the significance of an apical systolic murmur has changed in the course of the last 30 years and the present definition of an organic mitral murmur s a pan-systolic apical murmur audible o t in th left axilla differs from that in the beginning of th period covered by the present investigation. Since it was not possible to evaluat the significance of the murmu from the hospital records it was necessary to rely on the opinion of the clinician A systolic murm r *per se* in patients with cut rheumatic fever was not accepted as a sign f acut endocar ditis, except in a few cases, in which a ystolic murmur developed while the pat ent was under observation

During the years 1930—44 laboratory facilities were limited, therefore it was not possible to culture throat swabs or deter mine the antistreptolysin titre in suspected cases of rheumatic fever If a patient had tonsillitis before admission it was regarded as a minor manifestation even if the tonsillitis could not be related with certainty to previous streptococcal infection

In an unselected collection of cases of tonsillitis THULIN (1954) found throat swabs to give growth of beta hemolytic streptococci i 46.2 per cent and WINBLAD et al. (1017) found an elevated antistreptolysin titre in 82 per cent. It thus appears that the slight modification of the criteria is of only minor importance

The erythrocyte sedimentation rate is the only laboratory test that was used routinely during the entire study period therefore no other laboratory tests were used in the classification of the patients in the present investigation.

Since all cases of rheumatic fever even those in which the diagnosis was followed by a question mark were included, it was necessary t divide the series into 3 groups according t the firmness of th diagnosis from the notes in the record sheets of the patients — except those with a diagnosis of chorea mino which was classified as firm or probable according to the clinician s opinion. All patients satisfying JONES (modified) criteria were assigned to group A those with one major and only ne r no minor manifestation to group B those with no major manifestation but in wh m th clinical picture was such as to give reason to suspect the condition, to group C. These groups are referred to as the firm group (group A) the probable group (group B) and the suspected group (group C)

RHEUMATIC HEART DISEASE

The criteria suggested by the New York Heart Association (N Y.H.A.) i 1955 were used f r the diagnosis of rheumatic heart disease

AORTIC INCOMPETENCE (A.I.)

The diagnosis was made on the basis f the characteristic diastolic murmur which is high-pitched and blowing in

character and located in the left or the right third intercostal space Systolic murmur over the aorta may sometimes occur without being due to aortic stenosis. In advanced cases roentgenography will often show an enlargement of the left ventricle and electrocardiography left ventricular hypertrophy

AORTIC STENOSIS (A. S.)

Aortic stenosis is usually seen in association with incompetence of the aortic valves The diagnosis is based mainly on a systolic thrill in the right second intercostal space — though not necessarily — and a systolic murmur which is loudest in the right second intercostal space but which radiates over the entire thorax and up over the carotid arteries. Roentgen examination will often reveal an enlargement of the left ventricle and sometimes calcification at the site of the aortic valves, and electrocardiography left ventricular hypertrophy

MITRAL INCOMPETENCE (M. I.)

Mitral incompetence is characterised by a pan-systolic murmur best heard in the apical area and usually transmitted to the left axilla. Roentgen examination will often reveal enlargement of left ventricle and atrium, and electrocardiography often left ventricular hypertrophy

MITRAL STENOSIS (M. S.)

The characteristic findings are a loud snapping first sound and a split second with a low-pitched presystolic and/or early diastolic murmur often throughout diastole. The second sound over the pulmonary area is often accentuated. Roentgen examination usually shows an enlargement f the left atrium and in advanced cases of the right ventricle and a dilatation of the pulmonary artery Electrocardiography may show a right ventricular hypertrophy and larg notched P waves.

Tricuspid and pulmonary valvular lesions were diagnosed only in a few cases and then always on the basis of auscultation roentgenography and catheterisation.

COMMENTS

The criteria suggested by the N Y.H.A. in 1955 are also satisfied by other valvular deformities such as syphilitic arteriosclerotic and bacterial deformities and it is not always possible to distinguish them from rheumatic heart disease by clinical examination except the syphilitic cases which were excluded. Rheumatic heart disease (R.H.D.) is to be understood as chronic valvular heart disease of so-called rheumatic type while the acute form of R.H.D will be referred to as acute endo- myo- or peri-carditis.

As in the classification of cases of acute rheumatic fever attempts were made to assess the firmness of the diagnosis in rheumatic valvular disease from the notes in the record sheets of the patients. All patients with a diagnosis of R.H.D were divided into three groups. Group A 1 consisted of patients satisfying the criteria of the N Y.H.A. for a firm diagnosis. Group B-1 consisted of those patients in whom the diagnosis of R.H.D was probable but not firm because of doubtful auscultatory findings, e. g doubtful diastolic murmurs or systolic murmurs without roentgenographic or electrographic abnormalities. To group C-1 were assigned those cases in which the disease was less probable Patients with a diagnosis of rheumatic valvular disease were placed in this group if the auscultatory findings were not clear-cut, especially if the patient had coexistent hypertension thyrotoxicosis severe anaemia, or suspected congenital heart disease. According to the firmness of the diagnosis these groups are hereinafter referred to as: firm (group A 1) probable (group B-1) and suspected (group C-1).

In such a classification of the patients a certain overlapping of the groups must be expected. In addition, electocardiography and roentgenography were not so

common during the 30ies as in more recent years which means that some of the patients examined in the 30ies and assigned to group B-1 for example would have been allotted to group A 1 if they had been examined electrocardiographically and roentgenographically

At the re-examination only two groups were recognised namely certain R.H.D (satisfying the criteria of the N Y H.A.) and uncertain R H D i e where laboratory studies were inconclusive

METHODS AND MATERIAL

SELECTION OF CASES

In 1955 Malmö had a population of 209 4?3 inhabitants served by one hospital, Malmö General Hospital. The town has no private hospitals but before 1950 there was also a private children's hospital (Rönneholms clinic). The archives for 1930—54 of the departments of medicine infectious diseases, orthopaedics and paediatrics of Malmö General Hospital and of Rönneholms clinic were searched for the following diseases:

1) Acute rheumatic fever including such diagnoses as acute polyarthritis acute endocarditis and chorea minor

2) Rheumatic heart disease including such diagnoses as "vitium organicum cordis" but not syphilitic heart lesions or congenital heart disease.

During the years 1930—44 patients who died in the hospital were autopsied by competent pathologists from the department of pathology University of Lund and the findings were noted in the hospital sheets in Malmö. All patients from the departments of medicine infectious diseases orthopaedics and paediatrics with the above-mentioned diagnoses and autopsied during 1930—44 are included in the autopsy series. In 1944 a special department of pathology was opened in Malmö. From that time to 1955 it was possible to trace *all* dead patients from *all* departments of the hosptial with any of the above-mentioned conditions. These cases together with those admitted during 1930—54 and autopsied during 1955—58 are referred to as *the autopsy series*

Non-residents of Malmö referred to the hospital for examination or treatment, are not included in the material.

RE-EXAMINATION

During 1953 a total of 1 109 patients belonging to this material were re-examined at the heart laboratory The original purpose of the re-examination was to select patients for mitral surgery but the investigation was afterwards extended to include:

1) elucidation of the natural history of rheumatic fever
2) collection of information on the composition of the material of rheumatic heart disease
3) a "pilot" general heart examination on a selection of the population.

RE EXAMINATION METHODS

1) Analysis of previous hospital records. History: General medical special cardiologic social.
2) Complete physical examination.
3) Hemoglobin, blood count, urine analysis erythrocyte sedimentation rate (Westergren)
4) Electrocardiography During 1953 three standard extremity leads and one chest lead (V_4) but during 1954—59 12 lead unipolar electrocardiograms.
5) Full chest x-ray frontal and lateral, determination of heart volume.

In addition, if in lic ted

1) Unipolar lectrocardiogram — during 1953.
2) Antistrept l in titre Agglutination of sensitised heep cells.
3) Wasserma t t
4) Basal metabol h rate
5) Admission t hospital for observa tion.

The examination wa free of charge for the patients. Th v were invited by letter to come t the clinic The letter explained the purpose of the investigation and suggested a certai day and hour for the examin tion. I 1953 the team of xaminers consisted of G. Biörck, K. Bülow and th author After 1953 *all* the clinical examinations were performed by the a tho

During 1953 invitations were sent to 1,322 persons. 172 (13.0 per cent) were not reached and 41 (3.1 per cent) refused to co-operate and th remaining 1 109 patients were re-examined. These patients are referred to as *the clinical series.*

From 1950—58 a t tal of 83 patients were perated upon for mitral lesions, and this series is referred to as *the operated series*

TRACING OF PATIENTS

In the summer of 1958 the parish registers were studied to ascertain how many of the patients — re-examined or not — were still alive and how many had died in the meantime *i e* before January 1 1958

DATA ON POPULATION

Since the hospital material reflects the situation of the entire population data are given on the total number of inhabitants and the number of deaths per 5-year period in the town and in th hospital respectively during the years 1930—54

The mortality in Malmö decreased from 0.98 per cent in 1930 to 0.81 per cent in 1955. The number of deaths in the hospital in relation to the total number of deaths in the town increased from 24 7 per cent *in 1930 to 4 ~ per cent in 1955. The num*ber of autopsies in relation to the total number of deaths in the town increased from 28.8 per cent in 1945 to 44 4 per cent in 1955 and the corresponding figures for those who had died in the hospital were 81 6 per cent in 1945 90.5 per cent in 1950 and 93.1 per cent in 1955 No exact figures can be given for those who died in hospital before 1944 but the percentage of patients who died from rheumatic fever and rheumatic valvular disease will be given in the f llowing chapters.

The figures given above suggest that since half of all deaths in Malmö occur in hospital, and since the t wn has only one hospital in which about 90 per cent of all pati nts dying there are autopsied

Year	Inhabitants	Total Mortality	Died in hospital	Autopsied	Beds per 1 000 inhabitants
1930	120,304	1 184 (0.98)	293 (24 7)	—	3.8
1935	141 485	1,327 (0.94)	434 (32.7)	—	3.5
1940	153,506	1,534 (0.99)	453 (29.6)	—	3.2
1945	171 053	1 658 (0 97)	586 (35.3)	478 (28.8)	3.6
1950	192,498	1 689 (0.88)	624 (36.9)	563 (33.5)	3.6
1955	209 473	1 707 (0.81)	814 (47 7)	58 (44 4)	3.3

(Figures in brackets indicate percentages)

In departments studied, see page 12.

Malmö lends itself well to epidemiologic studies.

The number of beds per 1 000 inhabitants during the 25 years covered by the present investigation was highest in the years 1930—39 and lowest in 1940—44 when it was 3.2 per 1 000 inhabitants and then somewhat higher in 1945—55.

ELECTROCARDIOGRAPHY

The electrocardiograms were interpreted in accordance with the recommendations of GOLDMAN in Principles of Clinical Electrocardiography (1956). The electric axis was said to be normal deviated to the left or right according to the same pattern as that used by OLESEN (1955) and described by GOTZSCHE & WARBURG (1951). In outline this method implies that with knowledge of the QRS complex in the standard electrocardiogram, right axis deviation is defined as a negative QRS complex in lead I, a normal axis as a positive QRS complex in leads I and III with the exception that a negative QRS complex in the latter lead is regarded as a normal axis if the surface of the QRS in lead I is larger than in lead II and the surface of QRS in lead II is larger than in lead III. Otherwise the axis is deviated to the left provided that the QRS complex does not exceed 0.12 secs.

ROENTGENOGRAPHY

From the frontal and lateral views the total volume of the heart was calculated by the method of LYSHOLM, NYLIN & QUARNÅ (1934) and LILJESTRAND LYSHOLM NYLIN & ZACHRISSON (1939) and later modified by JONSELL (1939). The body surface was determined from the patient's height and weight, and from this the heart volume in ml per m^2 of body surface was calculated. According to MAURER NYLIN & SOLLBERGER (1955) the upper normal limit, as judged by this method is 450 ml per m^2 for females and 500 ml per m^2 for males. It should be pointed out that as shown by ARVIDSSON (1958) the relative heart volume may be within normal limits despite enlargement of the heart chambers. In mitral stenosis the relative heart volume may be normal with a bulgent left atrium and interpretation of the roentgenogram of the left atrium was made the subject of a special investigation (HALL et al. 1961) Pulmonary stasis and enlargement of the other heart chambers were judged by the principles laid down by the N.Y.H.A. (1955).

STATISTICAL METHODS AND CALCULATION OF SURVIVAL

The prognosis of R.H.D was judged by the method used by OLESEN (1955) and described by BERKSON et al. (1950) and BURCHELL et al. (1954).

A comparison of the morbidity rates in the different 5-year periods was made as follows. Consider a certain 5-year period and let p_1, p_2, ... be the morbidity rates in the different age groups. A standardised morbidity rate for this period was computed from the expression $w_1p_1 + w_2p_2 + ...$, where the weights w_1, w_2, ... denote the age-group distribution of the population of Malmö in 1955. This calculation was performed for each 5-year period, and the resulting standardised morbidity rates were compared. By this method, systematic errors due to changes in the age composition of the population were eliminated.

Ordinary statistical methods and abbreviations have been used (SNEDECOR, 1946).

REPRESENTATIVITY OF MATERIAL

For technical reasons only about half of the patients still alive on January 1 1958, were examined. It might therefore be objected that the material examined is not representative. The fact that only half of the patients were re-examined can,

however hardly influence any conclusions drawn because the selection of the patients was not such as to *bias th material.*

At the beginning of the investigation in 1953 *i e* when the main purpose of the re-examination was to select patients for mitral surgery patients treated in 1940—40 had a better chance of being re-examined than those treated in 1930—39 because they were easier to trace and secondly the chance of a patient with a firm diagnosis being re-examined was greater than that of a patient in whom the diagnosis w s doubtful and thirdly in 1053 more time was reserved for re-examination of the females than of the males. But this did not bias the material as far as the present investigation is concerned.

This is supported by th following check studies.

In 1058 all survivors who had had chorea (except 4 males living outside of Malmö and unable to spare th time for a re-examination but wh reported that they were in a good state of health) and all who had not been examined in 1953 were *examined It is clear from Figs. 1 and 2* that those re-examined in 1953 did not differ in age at the time of the first attack from those in 1958 (the mean age at the first attack was 10.3 years in 1953 compared with 9.5 years in 1958) but they did differ and considerably so concerning the year in which they had been admitted. The group examined in 19.3 belonged to a later period than those examined in 1958 and the interval between the first attack and the re-examination was shorter in the first mentioned group — 12.4 years and range 2—23 years — than in the group examined in 1958 — mean observation time 23.7 years and range 15—33 years. This might affect the results from a prognostic point of view since according to BLAND & JONES (1032) for example the frequency of R.H D increases with the interval between the attack and the review The results of the re-examination in 1953 and 1958 are summarised in p. 16.

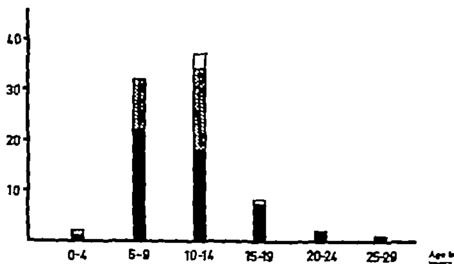


Fig. 1 *Chorea minor*

Classification of patients according to age on first admission

Re-examined in 1953 | Re-examined in 1958 | Not re-examined

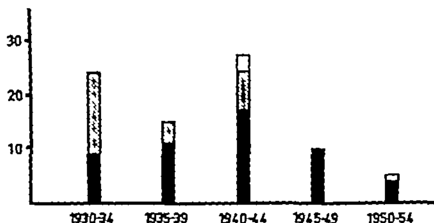


Fig. 2. *Chorea minor*

Classification of patients according to 5-year period

Re-examined in 1953 | Re-examined i 1958 | Not re-examined

COMPARISON BETWEEN 2 GROUPS OF PATIENTS WITH CHOREA MINOR

One examined in 1953 and the other in 1958

Year	Rheumatic heart disease Certain	Uncertain	Excluded	Total
1953	7 (13.7)	11 (21 6)	33 (64.7)	51
1958	5 (18.5)	6 (22.2)	16 (59.3)	27

(Figures in brackets indicate percentages)

Valvular disease appeared to be more common in the 1958 group but th differ ence was not significant (P > 0 05). Jud ging from this analysis then, there was no reason to suppose any appreciable differ ence between those examined in 1953 and those examined in 1958 In other words the group examined in 1953 appears to be representative It also appears that the number of patients in whom valvular complications occurred after 12.4 years on the average after the first attack, was low

As a further check up another group of patients was also examined. During the years 1945 –49 a total of 262 patients were admitted for acute polyarthritis. Of these 16 had died before January 1 1958 and 10 could not be traced 30 had moved out of town and 156 were re-examined in 1953 Of the remaining 50 patients 43 were re-examined in 1959 (6 would not co-operate of whom 4 would not co-operate in 1953 and 1 had died). The distribution of the groups examined in 1953 and 1959 is given in p 17

The only difference was, for reasons previously given (page 15) that group A — firm diagnosis of rheumatic fever — was larger and group B — probable rheumatic fever — smaller in 1953 than in the 1950 series. Group C contains the cases with suspected rheumatic fever Valvular disease was more common in the 1953 series (11 6 per cent against 7 0 per cent) because that series contained more

COMPARISON BETWEEN 3 GROUPS OF PATIENTS WITH ACUTE POLYARTHRITIS ADMITTED TO THE HOSPITAL IN [illegible]

One examined in 1953 and the other in 1959

Year	Group A		Group B		Group C	
	Number of patients	R H D	Number of patients	R.H D	Number of patients	R.H D
1953	98	16 (16.3)	51	2 (3.9)	6	0 (0.0)
1959	12	2 (16.7)	22	1 (4.5)	0	0 (0.0)

(Figures in brackets indicate percentages)

One patient was examined but data from the first admission were not available. The case could therefore not be grouped and is not included in the table

cases with a firm diagnosis of rheumatic fever. It is clear from the table that no difference was found between the groups regarding the frequency of R.H D.

HOW RELIABLE WAS THE CLINICAL DIAGNOSIS IN THE PATIENTS RE-EXAMINED IN 1953?

Of the patients in whom a diagnosis of R H.D had been made in 1953 51 died before 1958 and 20 of them were autopsied. The clinical diagnoses and the post mortem findings are compared below

Good agreement was found between the two types of diagnoses, though autopsy showed a few cases of stenosis only when the clinical diagnosis had been stenosis with incompetence

In the vast majority of cases the clinical and the post-mortem diagnoses were compatible. In one case however aortic incompetence had been incorrectly diagnosed clinically as mitral stenosis and in one case no definite clinical diagnosis had been possible

Clinical diagnoses		Post-mortem findings
M.S.	13	M.S. 12, A.I 1
M.S.M.I.	4	M.S. 3, M.S. A.I 1
M.S A I	3	M S. 1 M.S. A.I 1 M.S A.S. 1
M.S.M I A.S.A.I.	1	M.S. A.S 1
A.S.A.I.	2	A.I. 1 M.I A.S. 1
A.I.	2	A.I 2
non-specified	1	M.S M I 1

PART I

ACUTE RHEUMATIC FEVER

SURVEY OF LITERATURE

The literature in this field is far to voluminous to allow anything like a com plete survey This chapter will therefore be limited to a brief outline of relevant points necessary to facilitate understand ing of the analysis of the material. Ex cellent reviews of the American and Eng lish literature have appeared in Ann intern. Med. 1948 1953 and 1959

The terms "rheumatism and "rheumatic diseases are used to describe a large group of musculo-skeletal diseases with pain, impaired mobility of joints as well as swelling and other reactions of the joints and surrounding tissue (Rheuma tism and arthritis review of American and English literature of recent years 1959) The term rheuma was introduced by HIPPOCRATES, but it was not until the seventeenth century that acute poly arthritis was first described then by GUILLAUME DE BAILLOU Since then various subgroups have been recognized and according to the modern classification of American Rheumatism Association 1959 there are. 1) Diseases primarily related to trauma 2) Arthritis due to specific infectious agents 3) Rheumatic fever 4) Rheumatoid arthritis 5) Rheumatoid (ankylosing) spondylitis 6) Osteoarthritis (degenerative joint disease) 7) Backache and siatica 8) Gout and gouty arthritis.

HISTORICAL LANDMARKS

Although GUILLAUME DE BAILLOU gave his classical description of acute poly arthritis already in th seventeenth century the many names given to this disease show that it is not a well-defined clinical entity

Names such as rheuma rheumatismus polyarthritis acuta rheumatism BOUILLAUD's disease polyarthritis subacuta polyarthritis rheumatica acuta rheumatismus infectiosus rheumatismus verus morbus rheumaticus specificus have been used to designate the disease now called acute rheumatic fever In 1778 PITCAIRN showed that cardiac disease was more common in patients with acute rheumatic fever than in the population in general, and in 1840 BOUILLAUD presented the Law of Coincidence, according to which acute rheumatic fever is associated with heart changes and this coincidence is the rule rather than the exception. In 1835 Sir THOMAS WATSON reported that the disease was most common in child hood and that the risk of cardiac com plications decreased with increasing age of the patient. SYDENHAM described chorea minor during the seventeenth century but BRODIE was one of the first to observe the correlation between this disease and acute polyarthritis and endocarditis. The intimate correlation between these two diseases was, however established by the work of ROGER in the middle of the nineteenth century Although rheumatic nodules were described in 1812 by WELLS, it was not until 1881 that BARLOW and WARNER pointed out the correlation between nodules, chorea and acute rheumatic fever Erythema marginatum was first described in 1831 by BRIGHT who

had observed roseola annulata in chorea minor. The first monograph on rheumatic fever according to HEDLEY 1910 was published in 1888 by JOHN HAYGARTH who is claimed to have been the first to use the term acute rheumatic fever.

DEFINITION

In 1943 P UL stated that no exact definitions are available for acute rheumatic fever and at the same time pointed ut that it is not easy to define the disease because of the marked differences between the clinical evaluations of the disease. The sam author also questioned whether rheumatic fever was a single clinical entity or a complex of various entities. Criteria devised b JONES (1944) and afterwards modified and used in the present investigation (see Chapter n Definitions) have been gen rally accepted and have been used in several in estigations including the extensi e study of different forms of treatment f acute rheumatic fever in a co-operative study of the Medical Research Council of Great Britain and the American Council on Rheumatic Fever in 1955 and by many others (FEINSTEIN et al. 1959, CHANG et al. 1958). MITCHELL (1955) however warns against too generous (uncritical) use of the diagnosis rheumatic fever and concludes that "in medicine as in law the patient should be presumed innocent until proven guilty". WALLGREN (1957) claims that the diagnosis of rheumatic fever can often be made without difficulty but that the diagnosis must often remain uncertain and that acute polyarthritis should not be regarded a a major but as a minor manifestation while a previous attack of A.R.F r R.H.D should be classified as a major manifestation. FRIEDBERG (1959) approached the problem along the sam line and lik many others, pointed out that we still have no specific laboratory test for the disease and that if JONES' modified criteria be accepted the diagnosis must often be based on polyarthritis alone and since this disease seld m results in rheumatic heart disease it should not be called rheumatic fever but post streptococcal arthritis. HANSEN (1946) and FRIEDBERG (1959) have pointed out the many possibilities of other false diagnoses since we now know that polyarthritis occurs in association with L.E.D without skin manifestations in erythema nodosum in ulcerative colitis in sarcoidosis etc.

Classification has however proved difficult as is apparent from an investigation in Pittsburgh, in which only one of every 8 of 327 patients with so-called rheumatic diseases satisfied the classical criteria of rheumatic disease (COBB et al 1955).

The commonest source of error is said to be rheumatoid arthritis but the symptoms may also be so similar as to make differentiation impossible (SASLAW et al. 1954). KERSLEY (1954) found that of 750 patients with rheumatoid arthritis the onset in 38 was such a to be regarded as acute rheumatic fever. The pathognomonic feature of rheumatoid arthritis is said to be that the disease leads to joint deformity (SASLAW et al. 1954) which is also apparent from the criteria of the American Rheumatism Association 1957 even though joint deformity i not regarded as bligatory. It might also be pointed out that rheumatic fever as well as rheumatoid arthritis may be accompanied by the same eye changes, scleritis, episcleritis, conjunctivitis, uveitis and iritis (GODTFREDSEN 1954). However rheumatic fever can though rarely result in chronic arthritis as first pointed out by JACCOUD (1880) and later expanded upon by BYWATERS (1950) and THOMAS (1955). Chronic arthritis of th type described by JACCOUD is limited mainly to the joint capsules, which explains why it has been called chroni fibrous rheumatism.

Rheumatic fever is not the only joint disease that can give rise to so-called rheumatic valvular disease because BAUER et al. (1951) and BEDFORD et al. (1960) have shown that aortic incompetence and R.H.D are also seen in rheuma-

toid arthritis and BERNSTEIN et al. (1949) and GAMP et al. (1958) that R.H.D occurs in ankylosing spondylitis. BYWATERS (1950) concludes that "rheumatoid heart disease occurs though rarely and that chronic *post-rheumatic* arthritis (type JACCOUD) is an even greater rarity

It is not only rheumatoid arthritis and other chronic joint diseases that make a firm diagnosis of A.R.F difficult but also a number of other diseases (SASLAW et al. 1954 CASSELS 1958) The purpose of JONES modified criteria was to prevent the tendency to label as rheumatic fever any chronic febrile illness for which no obvious cause can be found. The difficulty in identifying the disease makes it difficult to compare figures on mortality and morbidity (WARD 1956)

Whether chorea minor should be regarded as rheumatic fever or not is debatable (PAUL 1943) because sex distribution of chorea minor differs from that of other manifestations of rheumatic fever (see below under "Sex distribution") However chorea minor is now widely accepted as a type of rheumatic fever (JACOBSSON 1946 GRAHAM 1955 and others)

INCIDENCE AND FREQUENCY

According to CLEMMESEN (1949) the frequency of A.R.F has gradually decreased and in Denmark where the disease is notifiable it fell from 20 per 10 000 inhabitants in 1900 to 6.3 in 1946 the corresponding figures for Copenhagen being 30 and 4 8 respectively EDSTRÖM (1935) gave an annual frequency varying between 2.28 and 5 01 hospitalised cases per 10,000 inhabitants in Sweden in the years 1901—1934 He found no substantial decline in the frequency during these years. Neither could JACOBSSON (1946) find any decline in the frequency of the disease during the years 1922—1942 in a children s hospital in Gothenburg. According to PAUL (1943) it has been necessary to use less exact methods in the assessment of the incidence prevalence and general importance of A.R F ATWATER (1927) found the mortality from the disease to decrease from 9 0 to 3.0 per 100 000 inhabitants during the years 1904—1923 but he adds that this decrease might in part have been due to modification of the classification. BACH et al. (1939) was unable to say whether the disease had increased or decreased but stated. "So far as the acute phases are concerned all clinicians agree that the type of case characterised by acutely swollen joints sour sweats and severe prostration is now rarely seen.

LEFF (1956) who reported mortality rates for A.R.F and rheumatic heart lesions in persons below 15 years in England and Wales found 1,251 in 1940 and in 1953 it was only 310 HITCHENS (1956) described a similar tendency for Cardiff during the 1931—50 period. Various other authors (WOLFF 1951 QUINN et al. 1951 WALLACE et al. 1955 HANSSEN 1957 WILSON et al 1958 and BYWATERS & THOMAS 1960) have also described the same downward trend According to FLEMING et al. (19.0) the incidence of A.R.F is 0.73 per 10 000 in Minnesota. Some authors (GLOVER 1943 HITCHENS 1956 and others) found the frequency of A.R.F to have decreased even during World War II while others (HARVING 1946 and HANSSEN 1957) reported an increase in Scandinavia. A.R.F is said to be more common in temperate climates which has been pointed out by PAUL (1943) and HOLBROOK (1944) and is apparent from the frequency of R H D in autopsy series from different parts of the world (CLAIBORNE & WOLFF 1941 GELFMAN 1943 DECHERD et al. 1943 HARRISON et al. 1924 and WAALER 1958) EDSTRÖM (1935) found a geographical variation in frequency of A.R.F in Sweden the disease being more common on the west coast than on the east.

LEWIS-JONSSON (1949) whose study of chorea minor covered the years 1910—44 found a downward trend of the frequency after 1920 without any upward swing of the frequency curve during the last War

A similar tendency was reported by KARLSTRÖM (1940) and JACOBSSON (1946).

SEX DISTRIBUTION

According to most authors (MACKIE 1926 McCUE et al. 1948 HARVING 1946 JACOBSSON 1946 and others) the disease is equally common in both sexes though some have found the frequency to be higher among females (EDSTRÖM 1935 ARNAO et al. 1951 and BACK et al. 1957)

Females are more apt to develop chorea minor than males (MACKIE 1926 PAUL 1943 JACOBSSON 1946) and LEWIS-JONSSON (1949) found 317 females and 150 males with rheumatic chorea, and the proportion of females to males in various reports is 1 7—2.4/1 (KARLSTRÖM 1940 HEDLEY 1940 BIÖRCK et al. 1955).

AGE DISTRIBUTION

A.R.F can occur at any age (BLAND & JONES 1952) but is most common in the ages between 5 and 15 years. EDSTRÖM (1935) found the frequency to be highest between 15 and 20 years and that more than 50 per cent were above 20 years at their first attack. JACOBSSON (1946) found the peak frequency to lie between 9 and 10 years and 50.5 per cent to be above 20 years when they sustained their first attack. The disease has been observed in advanced age (RAKOW & TAYLOR 1941 KJØRSTAD 1957 PADER et al 1959) as well as in infancy (DENENHOLZ et al. 1941 and DOMK et al. 1955)

RECURRENCES

The frequency of recurrences varies from one author to another Thus MACKIE (1927) gave 71 per cent, EDSTRÖM (1935) 50 per cent, ROTH et al. (1937) 68 per cent BLAND & JONES (1939) 66 per cent, WILSON (1940) 85 per cent, but the frequency appears to have decreased as pointed out by WILSON et al. (1958) and as is apparent from the investigation by BYWATERS & THOMAS (1958) in which recurrences were not more common in the first year after the attack than during the following 4 years of their study WILSON & LUBSCHEZ (1944) like EDSTRÖM (1935) and JACOBSSON (1946) however found the frequency of recurrences to be highest during the first year after the attack.

The risk of having a recurrence is said to vary inversely with age at the time of the first attack (MACKIE 1927 EDSTRÖM 1935 WILSON et al. 1944 and others)

The frequency of recurrences in untreated control groups in investigations of the value of prophylactic treatment is also low compared with the figures given above Thus STOLLERMAN (1954) found recurrences in 14.0 per cent of the untreated group against 1 9 per cent in the treated group WANNAMAKER et al. (1951) gave 3.0 and 0 0 per cent, respectively but BUNDY et al. (1952) found treatment with sulphonamides to lower the frequency from 61 per cent to 3.7 per cent.

AETIOLOGY

It is now generally accepted that group A hemolytic streptococci are the direct or indirect cause of A.R.F and thus ARNAO et al. (1951) and ROGERS (1958) found rheumatic fever to be preceded by tonsillitis in 48 and 49 per cent respectively The relationship between epidemics of streptococcal infections and outbreaks of A.R.F has been stressed by MADSEN & KALBAK (1940) MASSELL & JONES (1944) CATANZARO et al. (1954) and McCARTY (1956) and the relationship has been confirmed by the beneficial effect of sulphonamides and penicillin, for example (RAMMELKAMP 1958).

ANTISTREPTOLYSIN TITRE (AST)

In A.R.F the antistreptolysin titre is elevated in 70 to 96 per cent of all cases (KALBAK 1942, WINBLAD MALMROS & WILANDER 1949 McCARTY 1957 and ROGERS 1958) WINBLAD MALMROS & WILANDER found the AST to be higher in patients with A.R.F than in those

with uncomplicated streptococcal angina (tonsillitis) an observation confirmed by DENNY et al. (1950). TARANTA & STOLLERMAN (1956) showed that if three streptococcal antibodies (antistreptolysin, antihyaluronidase, antistreptokinase) were studied instead of one, the findings would be positive in all cases. The same author showed that "by the time chorea appeared these titres had fallen so that only four of ten patients still retained a high titer of antibodies

ERYTHROCYTE SEDIMENTATION RATE (E. S. R.)

In rheumatic fever the E.S.R. is elevated, and according to McCUE et al. (1948) the plasma fibrinogen is increased the gamma globulin level is high and the patient has anemia. DONOVAN (1958) reported an E.S.R. of more than 100 mm/1 hr but TARAN (1946) pointed out that rheumatic fever may be present even when the E.S.R. is normal. DEBRÉ et al. (1955) even claimed that an E.S.R. of more than 90 mm/1 hr was an important diagnostic sign. In pure chorea the E.S.R. is often normal (STOLLERMAN et al. 1953)

MORTALITY IN ACUTE RHEUMATIC FEVER

As mentioned by GRASER (1960) the mortality from acute rheumatic fever has decreased from 13.2 per cent to 2 per cent and HANSEN (1946) and MASSELL et al. (1958) even reported a mortality of less than 2 per cent.

The late mortality differs from series to series. BLAND & JONES (1952) gave for patients with the first attack of A.R.F before 20 years of age a mortality rate of 20 per cent after 10 years and 30 per cent after 20 years. EDSTRÖM (1935) found a total mortality of 9.. per cent but around 25 per cent for those with the longest follow up (33 years) while HANSEN (1946) found that 25—40 per cent died within 10 and 20 years respectively

FREQUENCY OF RHEUMATIC VALVULAR DISEASE AFTER ACUTE RHEUMATIC FEVER

According to most authors the frequency of R.H.D after A.R.F ranges between 50 and 70 per cent (EDSTRÖM 1935 JACOBSSON 1946 ASH 1948 BLAND & JONES 1952, RAMMELKAMP 1958 GRASER 1960) and the differences may be due to geographic differences but also to different criteria in the selection of the material as pointed out by RAMMELKAMP (1958)

A lower frequency of R.H.D after A.R.F was noted by ARNSO et al. (1951) and BJÖRCK (1955) who also found a difference between patients with a firm and doubtful diagnosis of A.R.F

It has been shown by JACOBSSON (1949) and BLAND & JONES (1952) that definite signs of R.H.D sometimes do not appear until several years after the acute attack. On the other hand, FEINSTEIN et al. (1959) believe that if there are no signs of heart disease at the end of an attack, no subsequent involvement of the heart need to be expected, and that it is therefore not justified to class all patients who have had A.R.F as having a "potential" heart disease.

The frequency of R.H.D is said to increase with every new attack of A.R.F (JACOBSSON 1946 BLAND & JONES 1952, and BJÖRCK 1955) while BROWN et al. (1940) claimed that "there is no constant relation between the severity of the illness or the number of recurrences and the development of cardiac damage GRASER (1960) could not find the frequency of R.H.D to increase with the number of attacks of chorea minor

Despite the voluminous literature that has appeared during the last few decades no reviews are available of the course of acute rheumatic fever over a number of years in one and the same population. Since the town is served by a single hospital (Malmö General Hospital) and since the population may be regarded as large enough for epidemiological studies it was considered worth performing an after examination of cases of acute rheumatic fever seen at the hospital during 1930—54

ACUTE RHEUMATIC FEVER

PRESENT MATERIAL

The number of patients with a diagnosis of acute rheumatic fever (A.R.F.) during the 1930—54 period was 1 434 of which the diagnosis was foll wed by a question mark in 147 (10.3 per cent). In the total material a linical diagnosis of acute polyarthritis + acut endocarditis + chorea minor was made in *2* patients acute polyarthritis + acute ndocarditis in *223* acut polyarthritis + horea minor in only *1* acute endocarditis + chorea minor in *15* acute polyarthritis only in *951* acute endocarditis only in *130* and chorea minor only in *81*. The total series is described in three parts (acut polyarthritis with a total of 1,208 patients acute endocarditis with a total of 371 patients and chorea minor with 100 patients) to reveal any differences which may otherwise be masked if all cases are simply dealt with under the common heading of A.R.F.

A. ACUTE POLYARTHRITIS

Analysis of th files f Malmö General Hospital f r the 1930—54 period revealed a total of 1,208 first admissions with a diagnosis of acute polyarthritis or acut rheumatic fever with symptoms and/or signs f joint changes. It should be stressed that this series includes all cases in which a diagnosis f acut rheumatic fever or acut polyarthritis had been noted in th hospital records. No patients with a diagnosis of subacut or subchronic polyarthritis were accepted. 95 cases (7.9 per cent) had a diagnosis with a question-mark on first admission. The distribution f the cases among 5-year periods is given in Fig. 3. Th numbers of admissions during the years 1930—34 1935—39 and 1950—54 wer roughly equal namely 220 210 and 12, while they were higher during the years 1940—44 and 1945—49 namely 304 and 282, respectively. By comparing the relativ number f admissions during 1940—44 to the average from the years 1935—39 and 1945—49 it was found that the increase during the war was significant ($P < 0.001$).

The most common diagnoses seen in association with the diagnosis of acute rheumatic fever namely acute endocarditis and rheumatic heart disease are given in Figs. 4 and 5.

Of a total of 1,208 cases of acute rheumatic fever 223 (18.5 per cent) had a *diagnosis of acute endocarditis*. The incidence of such cases in the 5-year groups were 32.3—20.5—19.4—11.8—9.0 per cent. Th frequency thus declined steadily throughout the period covered by the present investigation.

Of the patients with acute polyarthritis 4 also had chorea minor 5 also erythema marginatum and 5 also subcutaneous nodules.

Fig. 5 shows the distribution of 164 (13.6 per cent) cases with a diagnosis of acute rheumatic fever and chronic rheumatic heart disease. It is clear from th histogram that the frequency of the diag

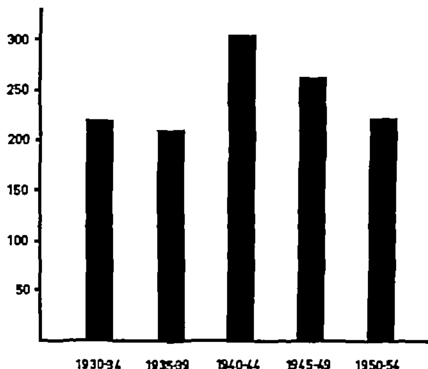


Fig. 3. *Acute polyarthritis.*
Total number of cases 1208
(Females 684 males 524)

nosis of rheumatic heart disease in association with acute rheumatic fever decreased steadily from one 5-year period to another 24 7—14.3—11 2—11.5—7 1 per cent.

INCIDENCE

Distribution of the diagnosis of acute polyarthritis per 10 000 inhabitants per year

1930—34	3.36	[220/131 000[1]]
1935—39	2.84	[210/148 000]
1940—44	3.73	[304/163 000]
1945—49	2.88	[262/182,000[1]]
1950—54	2.11	[212/201 000]

[1] Mean population of Malmo

Edström (1935) gives a frequency of 4.38 per 10 000 inhabitants in Sweden (mean calculated by present author) for the years 1930—34 The corresponding frequency for Malmö was 3.38 per 10 000. This difference may be due to geographical differences but also to the official figures being somewhat too high because the patient treated at different departments will be registered as different cases besides which each recurrence will also be registered as a new case.

The frequency of A.R.F during the years 1930—54 per 10 000 inhabitants thus tended to fall already during the 30ies, while it showed a peak during the years of the War 1940—44 During the last three 5-year periods the frequency decreased from 3.73 to 2.11 per 10 000 inhabitants. The total population and

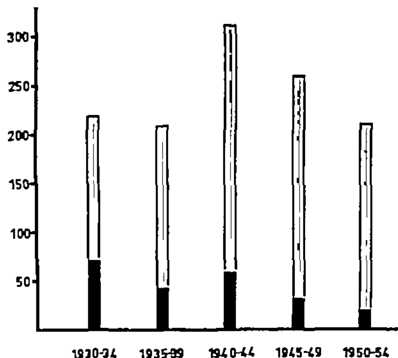


Fig. 4 *Frequency of acute endocarditis in patients with diagnosis of acute polyarthritis.*

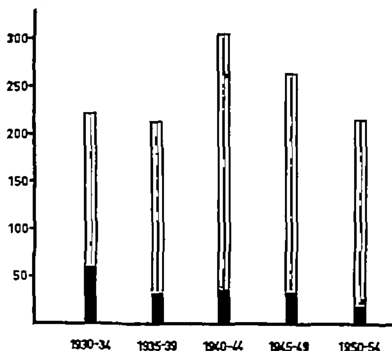


Fig. 5 *Frequency of rheumatic heart disease in patients with diagnosis of acute polyarthritis according to 5-year distribution.*

Table 1. Total population and incidence of acute polyarthritis per 5-year period in females grouped according to age.

Total number of cases 684

Period \ Age	0—9	10—19	20—29	30—39	40—49	50—59	≥60	Standardised morbidity rate
1930—34	7 674 *13* (1.7)	11,037 *33* (3.0)	15,868 *41* (2.6)	13,116 *21* (1.6)	10 637 *6* (0.6)	8,997 *4* (0.5)	8,582 *1* (0.1)	136.5
1935—39	8,990 *5* (0.6)	10,289 *31* (3.0)	16,282 *36* (2.2)	15,500 *17* (1.1)	11,654 *15* (1.3)	9 734 *11* (1.1)	10 402 *3* (0.3)	131.1
1940—44	12,466 *11* (0.9)	9,306 *28* (3.0)	15 643 *51* (3.3)	16,725 *43* (2.6)	13,420 *16* (1.2)	10 467 *10* (1.0)	12,812 *7* (0.6)	172.1
1945—49	15 452 *18* (1.2)	10,290 *22* (2.1)	15,447 *50* (3.2)	17,200 *42* (2.4)	15,969 *19* (1.2)	11,619 *9* (0.8)	15,138 *8* (0.5)	*161.0*
1950—54	15,074 *12* (0.8)	13,895 *15* (1.1)	13,960 *26* (1.9)	17 455 *24* (1.4)	17 488 *19* (1.1)	13,569 *8* (0.6)	17 731 *9* (0.5)	103.5

Figures in first row indicate number of inhabitants in Malmö.
Figures in italics indicate number of cases of acute polyarthritis.
Figures in brackets indicate number of cases of acute polyarthritis per 1 000 inhabitants.

Table 2. Total population and incidence of acute polyarthritis per 5-year period in males grouped according to age.

Total number of cases 524.

Period \ Age	0—9	10—19	20—29	30—39	40—49	50—59	≥60	Standardised morbidity rate
1930—34	8,021 *9* (1.1)	10 460 *34* (3.3)	13,097 *25* (1.9)	11 426 *16* (1.4)	8,992 *12* (1.3)	7,549 *2* (0.3)	6,214 *3* (0.5)	141.7
1935—39	9,294 *5* (0.5)	9,614 *28* (2.9)	13,693 *28* (2.1)	13,787 *13* (0.9)	10 038 *12* (1.2)	8,220 *4* (0.5)	7,919 *2* (0.3)	119.3
1940—44	13,035 *13* (1.0)	8,842 *38* (4.3)	13,192 *38* (2.9)	15,051 *26* (1.7)	11 720 *11* (0.9)	8,595 *7* (0.8)	9 779 *6* (0.6)	173.2
1945—49	15,958 *27* (1.7)	10 128 *22* (2.2)	13,925 *18* (1.3)	16,210 *13* (0.8)	14,185 *9* (0.6)	9 721 *1* (0.1)	11,396 *4* (0.4)	103.1
1950—54	15,934 *25* (1.6)	14 107 *26* (1.8)	13,003 *19* (1.5)	16,278 *12* (0.7)	15,682 *8* (0.5)	11 742 *4* (0.3)	13,335 *6* (0.4)	98

Figures in first row indicate number of inhabitants in Malmö.
Figures in italics indicate number of cases of acute polyarthritis.
Figures in brackets indicate number of cases of acute polyarthritis per 1 000 inhabitants.

incidence of acute polyarthritis per 5-year period in females and males and grouped according to age are given in Tables 1 and 2. The standardised morbidity rate gives a better idea of the frequency than does the number of cases per 10 000 inhabitants because this last mentioned method does not take into consideration the changes in the age distribution of the population. The standardised morbidity rate given to the right in th tables shows the f flowing values for females and males 278.2—2.0.1—315.3—204 1 and 202.2 for the respective 5-year periods. The differences in the frequ ncy of th disease between the years 1930—34 1935—39 and 1945—49 was negligible and the decrease during the 50ies was only slight. Th decrease in th frequency f diagnosed cases of acute polyarthritis during the last three 5-year periods n th other hand was not more marked than that calculated per 10 000 inhabitants per year It is thus remarkable that from 1930 to 1950 the frequency of the diagnosis of acute rheu matic fever as estimated from the composi tion of the hospital material was practically one and the same except for th years of the War and did not decrease until the 1950—54 period.

Of 1,208 patients data from the first attack during 1930—34 were available in 1 146 (94 9 per cent) In these cases it was possible to judge from the hospital records how many had not had their first attack but a recurrence in th years 1930—54

See page 14

90 (7 9 per cent) patients had thus had their first attack before 1930 The number of patients who were admitted during the various 5-year periods for their first attack in 1930—54 will therefore be as follows 168 172, 279 237 and 200 respectively and if the values are given in standardised morbidity rate 220.3—208.7—313 0—241 7 and 183.8 The number of cases with incomplete records was 62 and these patients were fairly evenly distributed among the 5-year periods (10—16—12—16—8) The figures given above thus refer to frequency of the first attack of A.R.F per 5-year period after correction for changes in age distribution of the population. The frequency did not fall below the value of 1930—39 before 1950—54 The figures also indicate that intervals of many years may occur between the attacks of acute rheumatic fever

FREQUENCY OF THE DIAGNOSIS OF ACUTE POLYARTHRITIS CLASSIFIED ACCORDING TO DEGREE OF FIRMNESS OF DIAGNOSIS

The firmness of the diagnosis in the 1 146 cases was judged according to the criteria given in page 10 62 (5 1 per cent) of the total material (1,208) could not be classified owing to the hospital records being incomplete The series was divided into three groups. A (firm diagnosis) B (probable) and C (suspected). 483 (42.2 per cent) patients were assigned to group A, 428 (37 4 per cent) to group B

CORRECTION FOR PATIENTS WITH FIRST ATTACK BEFORE 1930

Periods	1930—34	1935—39	1940—44	1945—49	1950—54
Total number of patients	210	194	292	248	204
With first attack before 1930	42 (20 0)	22 (11.3)	13 (4.5)	9 (3.7)	4 (2.0)

(Figures in brackets indicate percentages)

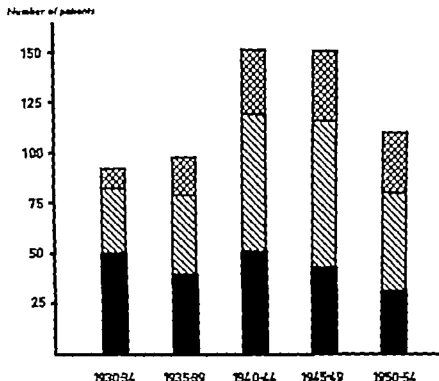


Fig. 6. *Acute polyarthritis.*
Classification of females according t firmness of diagnosi
Firm Probable Suspected
Total number of cases 598

and 235 (20 5 per cent) to group C. This implies that if JONES modified criteria be strictly observed, the diagnosis was firm in only about 40 per cent and probable in almost as many

The patients who had their first attack during or after 1930 are classified to the firmness of the diagnoses in Figs. 6 and 7 The frequency of females and males in group A total 412 was 87 (51 8 per cent) during 1930—34 4 (42.8 per cent) during 1935—39 109 (39 2 per cent) during 1940—44 75 (31 5 per cent) during 1945—49 and 67 (33.7 per cent) during 1950—54 It is apparent that the relative frequency of patients with a firm diagnosis diminished from one 5 year period to the next. It is clear that the total number of cases with firm diagnosis decreased but slightly namely from 74 in 1935—39 to 67 in 1950—54 The increase during 1940—44 was significant ($P < 0.001$). In group B total 413, the number of females and males was 55 (32.7 per cent) in 1930—34 73 (42.2 per cent) in 1935—39 107 (38.5 per cent) in 1940—44 104 (43.7 per cent) in 1945—49 and 74 (37.2 per cent) in 1950—54 Thus the relative frequency of cases with a probable diagnosis showed no tendency to increase or diminish during the observation period but the total number of cases was highest during the 40ies. The number of cases in 1935—39 was almost the same as in 1950—54 In group C total 231 the number of females and males was 26 (15.5 per cent) in 1930—34 26 (15.0 per cent) in 1935—39 62 (22.3 per cent) in 1940—44 59 (24.8 per

binding capacity in normals and in disease J.clin.Path. *5* 312 1952

DEMULDER, R. Iron. Arch.intern.Med. *102*:254 1958

DRABKIN D. L. and AUSTIN J H Spectrophotometric studies Preparations from washed blood cells Nitric oxide hemoglobin and sulfhemoglobin. J biol Chem. *112*.51 1935

ECKERSTRÖM, S. Fortsatta undersökningar över sideropeni hos åldringar Nord.Med. *24* 1843 1944

ECKLEBE, G. Die moderne Cyanhämiglobinbestimmung als klinische und poliklinische Standardmethode der Blutfarbstoffuntersuchung und der durchschnittliche Hämoglobingehalt der Bevölkerung. Dtsch.med.Wschr *84* 1531 1959

FORSSELL, J Morphologische Veränderungen in Knochenmark und Blut bei akuten Blutungsanämien. Acta med scand. suppl. 101 1 1939

FOWLER, W M. and BARER, A. P Plasma iron Normal values Response following medication. Amer J med.Sci. *223* 633 1952

FOY H. and KONDI, A. Nutritional and intestinal factors and iron losses in the genesis of tropical anaemias. Lancet I 423 1956

FREDRIKSON, K. A. Significance of serum iron in differential diagnosis between gastric carcinoma and peptic ulcer Acta med.scand. *146* 239 1953

GITLOW S. E. and BEYERS, M. R. Metabolism of iron. I Intravenous iron tolerance tests in normal subjects and patients with hemochromatosis J Lab.clin.Med. *39*:337 1952

GUPTA, S., KUMAR, S., DEVI, K. P and MANGALIK, V S. Studies in anemia of infection. I Plasma iron, iron-binding capacity of plasma and free erythrocyte proto-porphyrin in normal Indian subjects. Indian J med.Res. *47*/2 150 1959

HAGBERG, B. The iron-binding capacity of serum in infants and children. Acta paediat. *42*. suppl. 93 1 1953

HARJOLA, O Beitr z. Kenntnis d. peripheren Blutbildes während d. Schwangerschaft u. d. s. g. Graviditätsanämien. Acta obstet.gynec.scand. *26* suppl. 3 1 1946

HAWKINS, W W SPECK, E. and LEONARD, V G. Variation of the hemoglobin level with age and sex. Blood *9*.999 1954

HEILMEYER, L. and PLÖTNER, K. Das Serumeisen und die Eisenmangelkrankheit. Fischer Jena, 1937

HERMELLER, O Metabolisme du fer Physiologie pathologie-traitement. Masson & Cie Bd St. Germain, Paris, VI[e] 1951

HIRVONEN, M. Seerumiraunta ja infektiota dit. Duodecim *56*.535 1940

HURTADO, A., MERINO, C. and DELGADO, E. Influence of anoxemia on the hemopoietic activity Arch.Int.Med. *75*:284 1945

HYTTEN, K. Serumjernets fysiologiske variation. Universitetsforlaget, Aarhus, 1946

JERVELL, O and WAALER, G. H. M. En undersøkelse av haemoglobin hos 50 friske menn. Norsk Mag Laegevidensk. *95* 1141 1934

JUDY H. E. and PRICE, N. B. Hemoglobin level and red blood cell count findings in normal women. J.Amer med.Ass. *167*.563 1958

JARVINEN L., TAKKUNEN R., TIRALA, R. and HALLMAN N Haemoglobin level of Finnish children and the effect of iron therapy on low values. Ann.Paediat.Fenn. *6*.241 1960

KAADA, B Hemoglobin values in Norwegian refugees on arrival in Sweden Nord.Med *39*-1013 1946

KARVONEN, M. J PEKKARINEN, M., METSÄLÄ, P and RAUTANEN, Y Diet and serum cholesterol of lumberjacks. Brit.J Nutr *15* 137 1961

KEIDERLING, W (Editor) Eisenstoffwechsel, Beiträge zur Forschung und Klinik. Georg Thieme Verlag, Stuttgart, 1959

KILPATRICK, G. S. Prevalence of anaemia in the general population. A rural and an industrial area compared. Brit med.J II 1736 1961

KILPATRICK, G. S. and HARDISTY R. M. The prevalence of anaemia in the community Brit.med. J I 778 1961

KING, E. J and GILCHRIST M. Determination of haemoglobin Haldane haemoglobin standard compared with iron and gasometric estimation. Lancet *2* 789 1947

KOMMERELL, K. Die Bedeutung der Bestimmung der Eisenbindungsfähigkeit des Serums für die differentialdiagnostische Unterscheidung der einzelnen Hyposiderinämieformen und für die Kontrolle der Auffüllung der Eisenspeicher unter therapeutischer Eisenzufuhr Z ges.inn.Med. *10*: 801 1955

LAURELL, C. B Studies on the transportation and metabolism of iron in the body Acta physiol.scand. *14* suppl. 46 1 1947

LAURELL, C.-B. Plasma iron and the transport of iron in the organism. Pharmacol.Rew *4*.371 1952

LINDSTRÖM, K. and TALLQVIST T W Den normala blodbilden hos fullvuxna finländare med beaktande av variationer beroende på kön, ålder och bosättning i stad eller å landsbygd. Finska Läk.-Sällsk.Handl. *65*.696 1923

LYNGBERG, L. L. and SCHARTUM-HANSEN, H. Blodets hemoglobinmengde og de røde blodlegemers antall og volum hos friske menn og kvinner Norsk Mag.Laegevidensk. *96*.832 1935

LUNDSTRÖM, P Studies on erythroid elements and serum iron in normal pregnancy Acta Soc. Med.upsalien. *55* 1 1950

LÖVGREN, O. Studien über den intermediären Stoffwechsel bei chronischer Polyarthritis. Acta med. scand. *47* suppl. 165 1 1945

MAKIDIS, S. and MICHAEL-KARAGEORGOPOULOU, C. Normal haemoglobin values for both sexes in Greece as determined by the cyanmethaemoglobin method (study made on 1278 healthy persons). Acta microbiol.Hellenica *3*.29 1958

STANDARDISED MORBIDITY RATE

Period	1930—34	1935—39	1940—44	1945—49	1950—54
Females	110 2	108.2	157.3	144 2	97 1
Males	110.1	100 5	155 7	97 5	91

SEX DISTRIBUTION

Of the 1 208 patients 684 (56 6 per cent) were females and 524 (43.4 per cent) were males. The standardised morbidity rate however gives a better picture of the sex distribution (Tables 1 and 2) and if only those patients be considered who had their first attack of A.R.F during or after 1930 and whose histories were known it will give the above-mentioned figures.

This material consisted of 1 056 patients 598 (56.6 per cent) females and 458 (43.4 per cent) males. There was a slight preponderance of females in all 5-year periods except for the years 1945—49 when the difference was considerable

The sex distribution of the patients in groups A B and C is given in Table 3. In group A the ratio of females to males was. 1/0 8 during 1930—34 1/0.9 during 1935—39 1/1 1 during 1940—44 1/0 7 during 1945—49 1/1 1 during 1950—54 and the overall sex distribution was 1/0 9 If corrected for the sex distribution of the population, this difference will not be significant. The corresponding figures for group B were 1/0 9 during 1930—34 1/0 9 during 1935—39 *1/0 6* during 1940—44 *1/0 5* during 1945—49 and 1/0 7 during 1950—54 In this group the sex distribu tion differed significantly ($P < 0\ 001$) between the periods in the 30ies and during the years 1950—54 compared with 1940—49 It should be observed that the sex differences occurred not only during the years of the War but also during the entire 40ies The ratio of females to males in group C was 1/0 8.

AGE DISTRIBUTION

The age distribution of the 1 208 patients admitted during 1930—54 shows two

Table 3. Classification f females and males according t age and firmness f the diagnosis f acut polyarthritis.

Age in years	Group A		Group B		Group C	
	F	M	F	M	F	M
0—4	3— 1.4	3— 1.5	4— 1 6	2— 1.2	4— 3.1	5— 5.0
5—9	22— 10 1	22— 11.3	16— 6.4	20— 12.3	9— 6.9	25— 24.8
10—14	30— 13.8	40— 20.6	18— 7.2	31— 19 0	7— 5.4	7— 6 9
15—19	20— 9.2	33— 17 0	18— 7.2	16— 9 8	14—10.8	7— 6.9
20—24	32— 14 7	23— 11.9	43— 17.2	19— 11 7	12— 9.2	7— 6 9
25—29	28— 12.8	32— 16 5	50— 20 0	22— 13.5	15—11 5	6— 5 9
30—34	28— 12.8	10— 5.2	46— 18.4	15— 9 2	14—10 8	8— 7 9
35—39	20— 9 2	14— 7 2	13— 5 2	14— 8.6	7— 5 4	6— 5 9
40—44	11— 5.0	8— 4 1	13— 5 2	11— 6.8	13—10 0	5— 5 0
45—49	8— 3 7	3— 1 6	11— 4 4	4— 2.5	5— 3.8	6— 5.9
50—54	8— 3.7	4— 2.1	9— 3.6	0	9— 6 9	5— 5 0
55—59	4— 1.8	1— 0 5	4— 1 6	3— 1 8	6— 4 6	3— 3 0
≥60	4— 1 8	1— 0 5	5— 2 0	6— 3.7	15—11 5	11— 10.9
Total	218—100 0	194—100.0	250— 100 0	163—100 1	130—99 9	101—100 0

Milam, D F and Muench, H.: Hemoglobin levels in specific race, age and sex groups of normal North Carolina population. J Lab. clin.Med. 31:878 1946

Moore, C. V The importance of nutritional factors in the pathogenesis of iron deficiency anemia. Amer J.clin.Nutr 3:3 1955

Moore, C. V Arrowsmith, Wm. R., Quilligan J J and Read, J T Studies in iron transportation and metabolism I. Chemical methods and normal values for plasma iron and easily split off blood iron. J.clin.Invest. 16:613:1937

Moore, C. V and Dubach, R. Physiology of iron metabolism Resorption, conservation, elimination and physiological iron losses. Eisenstoffwechsel, p. 112, Georg Thieme Verlag, Stuttgart 1959

Moore, C. V and Dubach, R. Observations on the absorption of iron from foods tagged with radioactive iron. Trans A. Amer.Physicians 64 245 1951

Morris, F K., Loy V E., Strutz, K. M., Schlossberg, L. L. and Schilling, R. F Hemoglobin concentrations as determined by methemoglobin method. Amer J clin.Path. 26 1450 1956

Mukherjee, C. L. and Mukherjee, S K.: Studies in iron metabolism in anemias in pregnancy II. Iron binding capacity and iron saturation of plasma. J Indian med.Ass 23 1 1953

Natvig H. Hemoglobinverdien hos voksne. Liv og Helse 27 171 1960

Nilsson, F Anaemia problems in rheumatoid arthritis. Acta med scand. 130: suppl. 210 1 1948

Nyberg, W Gräsbeck, R., Saarni, M. and Bonsdorff B. von Serum vitamin B₁₂ levels and incidence of tapeworm anemia in population heavily infected with Diphyllobothrium latum. Amer J.clin.Nutr 9:606 1961

Pekkarinen, M Tutkimuksia maalaisvaeston ravinnosta eraissa Ita ja Lansi-Suomen pitajissa. Acta Agralia Fennica, 99:5 1 1962

Peters, T Giovanniello, T J Apt L. and Ross, J F A new method for the determination of serum iron-binding capacity I J Lab.clin. Med. 48:274 1956

Peters, T Giovanniello, T J Apt L. and Ross, J F A simple improved method for the determination of serum iron. II. J.Lab.clin. Med. 48:280 1956

Pett L. B. and Ogilvie, G F Haemoglobin levels at different ages. Canad.med.Ass.J 58 353 1948

Pirrie, R. Influence of age upon serum iron in normal subjects. J.clin.Path. 5 10 1952

Pirzio-Biroli, G Bothwell, T H. and Finch, C. A. Iron absorption II. The absorption of radioiron administered with standard meal in men. J.Lab clin.Med. 51:37 1958

Powell, J E. Serum-iron in health and disease. Quart.J.Med ser 37 13 1944

Pätiälä, J: Untersuchungen über das weisse Blutbild und das Sternalpunktat bei primärem Lungenkarzinom. Acta tuberc.scand. 22. suppl. 28:1 1951

Ramsay W N M.: Plasma iron. Advanc.clin. Chem. 1 1 1958

Rath, C. and Finch, C.: Chemical, clinical and immunological studies on the products of human plasma fractionation. XXXVIII Serum iron transport. Measurement of iron binding capacity of serum in man. J.clin.Invest. 28 79 1949

Rechenberger, J Über die Eisenbindungskapazität des Blutserums in den verschiedenen Lebensaltern. Z. Alternsforsch. 9:98 1955

Rurtong, E. Studies of serum iron. Acta derm. venereol. 29: suppl. 21 1 1949

Sakakura, J Studien über den Eisengehal des Menschenserums im normalen und pathologischen Zustande, uber den Serumeisengehalt beim gesunden Japaner und beim gewerblichen Blutspender Tokyo Igakkwai Zassi 54:225 1940

Schales, O Iron in serum. Standard methods of clinical chemistry II 69 Academic Press, New York 1958

Schales, O The determination of serum iron. Klett-Summerson Photoelectric Colorimeter Manual, Klett Mfg Co., New York 1939

Schoenneider, P Serumeisen bei gesunden Frauen und in der Schwangerschaft. Arch. Gynak. 175 1 1944

Setälä, A. Studies on the haemoglobin values of the blood and on anaemia in the population of the Karkölä district. Ann.Med.intern.Fenn. 38 suppl. 4 1 1949

Sharpe, L. M., Peacock, N C., Cooke, R. and Harris, R. S The effect of phytate and other food factors on iron absorption. J.N tr 41:433: 1950

Skouge, E. Klinische und experimentelle Untersuchungen uber das Serumeisen. Videnskaps-akademiens (Oslo) Skrifter Mat.Natv.kl. Bd, 1 No 7 1 1939

Stewart, J M. and Schrade, A. L. Diurnal-nocturnal variations of certain blood constituents in normal human subjects. Brit.J.Haemat. 3 117 1957

Straus, W Fattal, B. and Shoha S. A survey of hemoglobin levels in Israel, 1959/60 J med. Ass. Israel. 62 113 1962

Straus, W Shaton-Hershberg, M and Bortten E. Nutritional survey in Israel, second interim report-surveys of 1951 and 1952 – 3. The Hebrew University-Hadassah Medical School, Jerusalem, 1954

Turpeinen, O Tutkimus normaalisen kansanravinnon sisaltaman raudan maarasta ja riittavyydesta. Duodecim 60 suppl. 3 1 1944

Tötterman G Über Sternalmark u. Blut bei Wurmträgern. Acta med scand. suppl. 104 1 1939

Totterman, L. E. Vitamin C and iron metabolism. Acta med.scand. 134 suppl. 250 1:1949

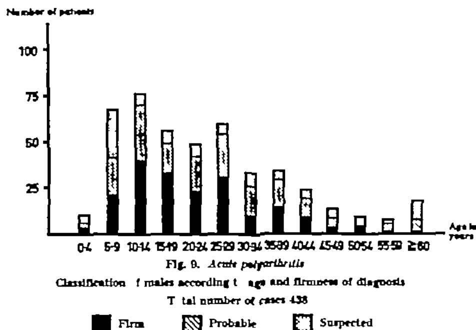


Fig. 9. *Acute polyarthritis*

Classification f males according t age and firmness of diagnosis

T tal number of cases 438

Firm Probable Suspected

25 1 years. The age distribution of the males in this group was about the same as that of the males in group A and the majority of the patients fell within the age limits 5 and 30 years, with two frequency peaks one between 10 and 14 years and the other between 25 and 29 years. The age distribution of the females showed only one peak between 20 and 35 years, and 55.5 per cent were within these age limits at the time of the first attack. The age distribution of group C, in which the subjects had only suspected A.R.F was fairly even, except for boys between 5—0 years and several patients were above 60

Tables 1 and 2 give the ages of the females and the males and the ages at the time of the first attack during 1930—54 Only those patients whose histories were known, were accepted. There were all together 1 056 cases. The tables give the age distribution for every 5-year period and the frequency appears to be fairly constant except for the 20—39 year group of women during the 1940—49 period and for the 10—29 year group of men during the years 1940—44 during which it in creased. The tables also show that the fall in frequency during the last 5-year period was due mainly to a fall in the 10—29 year group and to a certain extent in the 30—39 year group

FREQUENCY OF RECURRENCES

The patient was said to have a recurrence if he sustained an attack after a free interval of at least 6 months with a normal E.S R. Of the 1 146 patients whose histories were known, one or more re currences had occurred in 151— 5 females and 6 males—or 13.2 per cent. The average ages at the time of the first attack were 15.5 and 16.0 respectively and the mean ages at the time of the second attack were 26.5 and 26.5 years. A third attack occur red in 50 patients at an average age of 27 0 and a fourth in 12 patients at an average age of 30 years.

Of the 151 patients then 77.5 per cent belonged to group A (58 females and 59 males) 15 2 per cent to group B (14 females and 9 males) and despite recurrences 7.3 per cent belonged to group C (3

Vahlquist B. Das Serumeisen. Acta paediat. *28* suppl. 5 1 1941
Vahlquist B. and Neander, G. Har kriseden inverkat på normalvärdena for hämoglobin och roda blodkroppar Svenska Läk. Tidn. *41* 1327 1944
Waldenström, J. Incidence of iron deficiency (sideropenia) in some rural and urban populations. Acta med scand. *124* suppl. 170 1 1946
Wallerstein, R. O and Mettier, S. R. (Editors) Iron in clinical medicine. University of California Press, Berkeley and Los Angeles, 1958
W... Höckert O. and Eklund, J. Om järnbristanemi hos flickor i läroverksåldern. Finska Läk.-Sällsk. Handl. (In press)
Ventura, S. and Klopper, A. Iron metabolism in pregnancy The behaviour of haemoglobin, serum iron, the iron-binding capacity of serum proteins, serum copper and free erythrocyte protoporphyrin in normal pregnancy J. Obstet. Gynaec.Brit.Emp. *58* 173 1951
Werdenitz, E. Studien über die im nördlichsten Schweden gewöhnlichen Anaemiezustände. Lund, 1953 Håkan Ohlssons Buchdruckerei.
Verloop M. C., Blokhuis, E. W. M. and Bos, C. C. Causes of the differences in haemoglobin and serum-iron between men and women. Acta haemat. *21* 199 1959
Vinke M. Untersuchungen uber d. Einfluss d. Tonsillitis u.d. Tonsillektomie auf d. Sternalpunktat u.d. Blutbild. Acta med.scand. suppl. 146:1 1943
Who Study Group on iron deficiency anaemia. Iron deficiency anaemia. Wld Hlth Org. techn. Rep. Ser *182*, 1 1959
Zizza, F and Block, M. The interrelationship of the serum iron, iron binding capacity and tissue iron. Acta haemat. *25* 1 1961

No satisfactory explanation can be offered for this phenomenon. The range of the E.S.R. was wide between 18 and 146 in group A, 12 and 112 in group B and normal to 138 in group C.

ANTISTREPTOLYSIN TITRE

The antistreptolysin titre (AST) was determined at the department of bacteriology by the method described by WINBLAD (1941)

Since the sampling was not performed according to uniform principles during the 1944—54 period the AST will only be briefly dwelt upon. Of the 144 determinations made in group A 16 (11 1 per cent) showed a titre of less than 200 14 (9 7 per cent) between 200 and 300 76 (5..8 per cent) between 300 and 800 and 38 (26.4 per cent) above 800 In group B in which 142 determinations were made, the corresponding figures were 56 (39.4 per cent) below 200 46 (32.4 per cent) between 200 and 300 28 (19 7 per cent) between 300 and 800 12 (8.5 per cent) above 800 The figures for 54 cases in group C were: 26 (48.. per cent) 16 (29 6 per cent) 6 (11 1 per cent) and 6 (11 1 per cent)

It is thus obvious that normal values were found in 11 1 per cent in group A which is in good agreement with that found by WINBLAD (1941) and WINBLAD et al. (1949) in 39 4 per cent in group B and in 48.2 per cent in group C while values of more than 300 units occurred in 70 2 per cent 28 2 per cent and 22.2 per cent respectively

TRACING OF PATIENTS

Th number of patients still alive on January 1 1958 was ascertained from a search of the parish registers. No data could be obtained on 108 patients (8.9 per cent) mainly because of incomplete primary data in the hospital records. It is clear from Tables 4 and 5 that most of these patients had been cared for during the period 1930—44 *i.e.* during the first *three fifths of the period covered by the* present investigation.

MORTALITY

Of the 1 100 patients who could be traced out of 1 208 96 (8.7 per cent) had died in the meantime. The distribution of these patients according to time of their first admission to hospital during the period covered by the investigation is apparent from Tables 4 and 5 45 of the above-mentioned 96 patients had died at home 41 had died in hospital and 32 had been autopsied The mortality during the follow-up of 3—28 years was thus 8.7 per cent, but the mortality during an acute attack of rheumatic fever was only 1.5 per cent, *i e* 16/1 100

Of group A — with a firm diagnosis of rheumatic fever — 41 patients had died *i.e.* 8.5 per cent while during an acute attack of the disease only 6 (1 2 per cent) had died. The mortality during the acute phase and during the respective 5-year periods was as follows 2 1 2, 1 and 0

Of 6 patients 5 died during the first attack, 1 at the age of 4 years, 2 between 5 and 9 years, and 2 between 10 and 14 years. The remaining patient (case 1436) who died in 1931 at 63 years, had known valvular lesion and died during an attack of A.R.F but autopsy showed M S. M.I and congestion. Of the other 5 patients who had died 4 were autopsied. 2 of them (cases 1736 1752) aged 6 and 10 died in 1944 and 1930, respectively had minimal valvular changes but pericarditic adhesions and microscopic Aschoff granulomas, while the other 2 (cases 1749 1750) who died at 4 and 10 years in 1939 and 1946, respectively had marked pancarditis. The patient (case 3066), who was not autopsied, died at 8 years, in 1941 and had chorea and acut endo- and polyarthritis and died in sepsis.

Thus, of the 252 females and 231 males with firm diagnosis of rheumatic fever 5 and 1 (2 0 and 0 4 per cent) respectively died.

In group B — probable A.R.F — 12 (2.8 per cent) patients had died and none during the acute phase of the disease.

In group C — suspected A.R.F — 37

of hypertrophy B.P 145/35. Lab data: E.S.R. 20 and 19 mm./1 hr AST 250 U WBC 7,000 and 11 600. Blood culture gave no growth.

Autopsy The heart was markedly enlarged and weighed 570 g. The aortic valves were thick and swollen and showed small ulcerations and erosions in the free edges while the mitral valves showed less pronounced changes but with thickening of the chordae tendineae. The peri cardium showed fresh fibrin deposits. Micro-scopi examination showed a marked deposition of round cells in the endocardium and myocar dium as well as several Aschoff granulomas.

Diagnosis: Acut rheumatic fever Aortic in-competence.

Case 3025 A 37 year old man who had alway felt well, was admitted because of pulmonary oedema. During the previous few years he had had increasing shortness f breath and 3 weeks before dmission he had had fever and sore throat. One week later joint pain occurred — without swelling — which migrated from one joint t another

On admission he was ill with marked dyspnoe and pronounced leg oedema. Owing to the pul-monary râles no heart sounds or murmur were heard on admission or later in hospital. B.P 250/140 220/150 Electrocardiography showed sinus tachycardia with left axis deviation and marked negative T waves in leads I and V1 t V7 inclusive. Lab data: E.S.R. 74 mm/1 hr WBC 14,800 16,200. Proteinuria, Urin. sed. 5—10 whit and 5—8 red blood cells. AST 900 U Culture f throat sw bs gave no growth. *Autopsy Markedly enlarged heart (540 g)*, particularly the left ventricle. Valves of normal gross and microscopical appearance without signs of endocarditis. Recent fibrin deposits in pericardium and pleurae. Microscopical appear ance of heart, lungs and kidneys showed changes f the type seen in lupus erythematodes dissemi natus.

Thus, 1 2 per cent of group A died during the acute phase of A.R.F., 0 0 per cent in group B and 3.4 per cent in group C. The last-mentioned group consisted only of suspected cases and autopsy confirmed the suspicion in only 1 out of 8 The mortality during the acute phase tended to decline because only 2 patients died during the last two 5-year periods as against 6 in the 3 preceding 5-year periods.

The total mortality was 8.5 per cent in group A, 2.8 per cent in group B and 15 7 per cent in group C so that the late mortality was 7 3 2.8 and 12.3 per cent respectively

RESULTS OF RE EXAMINATION IN 1953 OR LATER

In 1953 or in the 1955—58 period 562 patients were after-examined represen ting 46.5 per cent of the entire material (1,208 cases) and 56.0 per cent of those who were still alive or who could be traced in 1958. The frequency of R.H.D in the examined group was 12.3 per cent while 73.5 per cent were judged as having no heart disease. The uncertain group of R.H.D contained 14 2 per cent which could not be classified as normal because of auscultatory electrocardiographic or roentgen findings. This group made a special study necessary and the results will be published elsewhere (Hall et al. 1961)

RESULTS OF RE-EXAMINATION OF PA-TIENTS CLASSIFIED ACCORDING TO FIRMNESS OF DIAGNOSIS

RHEUMATIC HEART DISEASE, CERTAIN

Table 6 shows that within group A — firm diagnosis — 53 or 19 7 per cent of 269 examined had R.H.D The distribu *tion of R.H.D among the females* and males showed a frequency of 22.5 and 16.8 per cent respectively but the difference was not significant. The observation period varied from 3 to 72 years and the number of person years was 3 660 calculated from the first attack of rheumatic fever

In the group with the probable diagnosis — group B — the frequency of R.H D was 7 0 per cent the frequency for females 6.1 and for males 8.2. The observation period varied from 1 to 51 years and the number of person years was 2 142 as cal-culated from the first attack of A.R.F

In the suspected group — group C — R.H.D was found in only 1 of 77 examined. This case is described in brief below

Case 1373. A 7 year old girl, whose father had rheumatic heart disease was admitted be-cause of acute tonsillitis and arthralgia. Exami nation revealed suppurative tonsillitis, but other wise nothing of interest. Heart sounds normal,

probable diagnosis of A.R.F and the difference, whether the two groups be taken together or each by itself, was almost significant ($P < 0.05$).

Of the uncertain R.H.D because of roentgen findings all the 17 females showed a slight bulge of the left atrium but in 2 there was also a relative enlargement of the heart. In none could any left ventricular enlargement be demonstrated. Of the 21 female uncertain cases, 5 were re-examined 4—6 years after the first examination. None of them showed definite signs of R.H.D Of 10 patients (4 females and 6 males), who had roentgen findings only R.H.D could be dismissed in all of them 4 years after the first examination.

In the group with suspected A.R.F — group C — there were 10 (13.0 per cent) with a diagnosis of uncertain R.H.D., 2 because of auscultatory findings (both females) and 8 because of roentgen findings. None of these patients were re-examined after 1953.

The mean observation time interval between the first attack and the first re-examination was 16.3 years in the group with certain R.H.D., 11 7 years in the group with uncertain R.H.D and 13.6 years in the group with excluded R.H D

B. ACUTE ENDOCARDITIS

Analysis of the files of Malmö General Hospital for the 1930—54 period revealed a total of 371 first admissions with a diagnosis of acute endocarditis with or without associated symptoms or signs of acute polyarthritis. Patients with acute pericarditis or myocarditis were not included unless they showed evidence of acute endocarditis. 38 (10.2 per cent) patients had the diagnosis with a questionmark on first admission. During the respective 5-year periods from 1930 the numbers of admissions were 126 during the years 1930—34 69 during 1935—39 90 during 1940—44 61 during 1945—49 and 25 during 1950—54 By comparing the relative number of admissions during 1940—44 to the average from the years 1935—39 and 1945—49 it was found that the increase during the War was significant ($P < 0.001$).

The commonest diagnosis in combination with acute endocarditis was acute polyarthritis and the frequency of this diagnosis is given in Fig. 10 Of 371 patients, a diagnosis of acute polyarthritis had been made in 223 (60 1 per cent). The frequency of this diagnosis in the 5-year periods was 56.4—62.3—65 6—50 8 — 60 per cent. The frequency of joint symptoms showed no significant variation during the 25-year period, though the frequency of endocarditis with associated acute polyarthritis was highest during the last 5-year period.

Of a total of 371 cases 106 (28.6 per cent) had a diagnosis of chronic R.H.D on the first admission and the frequency in the 5-year periods was as follows: 40.5—42.0—25 6—29.5—20.0 per cent. It is thus evident that the frequency of the diagnosis of R.H.D in association with acute endocarditis declined.

A diagnosis of chorea minor was made in 15 (4 0 per cent) cases.

INCIDENCE

Distribution of the diagnosis of acute endocarditis per 10 000 inhabitants per year

1930—34	1 92	[126/131 000]
1935—39	0 93	[69/148 000[1]]
1940—44	1.10	[90/163 000[1]]
1945—49	0 67	[61/182 000]
1950—54	0 25	[25/201 000[1]]

The decrease in frequency of the diagnosis of acute endocarditis is thus marked during the 30ies and the decrease from

[1] Mean population of Malmö

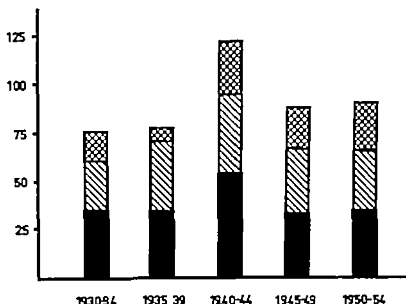


Fig. 7 Acute polyarthritis.

Classification of males according t firmness of diagnosis

Firm Probable Suspected

T tal number f cases 458

cent) in 1945—49 and 58 (29 1 per cent) in 1950—54 Thus the relative frequency f a firm diagnosis diminished from 50 to 30 per cent the probable group remained unchanged, and the suspected group in creased from 15 to 30 per cent.

The above-mentioned figures for the 5-year periods give the f llowing figures for the incidence per 10 000 inhabitants per year for acut polyarthritis in groups A—B—C.

Period	Group		
	A	B	C
1930—34	1 9	1 1	0.4
1935—39	1.2	1.2	0 4
1940—44	1.5	1.3	0 8
1945—49	0.9	1.2	0 7
1950—54	0 7	0.7	0.6

Group A — firm, B — probable and C — suspected rheumatic fever

For the group with a firm diagnosis of rheumatic fever according to Jones modified criteria there was a decrease from 1 9 to 0 7 per 10 000 inhabitants, and nly the 5-year period during th War showed a deviation from this tendency — the increase during 1940—44 was significant ($P<0.001$). For th group with probable A.R.F the frequency increased throughout the 40ies compared with that during the 30ies and it was not until 1950—54 that any ignificant decrease could be demonstrated ($P<0.001$). The group with only suspected A.R.F also showed a higher frequency during the 40ies than during the 30ies while the frequency tended to decrease during the last three 5-year periods. Control analysis using the standardised morbidity rate yielded no further inf rmation.

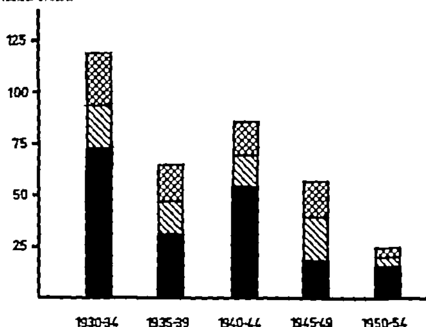


Fig 11 *Acute endocarditis.*
Classification according to firmness of diagnosis.
Total number of cases 350.

in the frequency of A.R.F during the War was mainly due to an increase in group A. Group B and C remained constant until 1950 when both showed a substantial decline The increase for group A during the years of the War was significant (P < 0 001)

Period	Group		
	A	*B*	*C*
1930—34	1 12	0.31	0.38
1935—39	0 42	0.22	0.24
1940—44	0 68	0 17	0 21
1945—49	0 20	0 22	0.21
1950—54	0 16	0 03	0 05

Group A — firm B — probable and C — suspected rheumatic fever

The above mentioned figures give the frequency of the different groups per 10 000 inhabitants per year for the different 5-year periods.

For the group with a firm diagnosis of acute rheumatic fever there was a striking decrease during the 30ies and then an increase. During the last two 5-year periods the incidence of acute endocarditis was low and with a downward trend. In group B — probable and in group C — suspected acute rheumatic fever the frequency decreased during the 30ies, was unchanged 1940—49 and then decreased markedly

SEX DISTRIBUTION

Of the total of 371 patients (177 females and 194 males) 18 of the females and 20 of the males had the diagnosis with a question mark.

In group A males were also preponderant (85 females and 108 males) as well as for

Age in years	0—4	5—9	10—14	15—19	20—24	25—29	30—34
Number of cases	23	115	141	130	154	183	133
Per cent	1.9	9.5	*11.9*	10.8	12.7	*15*	11.0

Age in years	35—39	40—44	45—49	50—54	55—59	≥60	Total
Number of cases	90	76	51	30	23	47	1,208
Per cent	7.5	6.3	4.2	3.2	1.9	3.0	100.0

peaks one between 10—14 years and the other between 25—29 years (see above and Table 3).

The initial attacks recorded in the high age classes during the years 1930—54 may be explained in part by some of the patients having had their first attack before 1930.

Figs. 8 and 9 give the age distribution of females and males whose histories were known and who had not had any known attack of A.R.F. before 1930. There was a marked difference between the females and males, the maximum for the males occurring in the 10—14 year class and for the females in the 20—34 year classes.

Group A contained only few patients below 5 years of age, 1.4 per cent for females and 1.5 per cent for males, and in both sexes between 10—14 years there was a peak, after which the frequency fell again. The figures showed a new peak at 20—24 years for the females and 25—29 years for the males. It should also be observed that the number of females in each age class between and 40 years varied between 20 and 30, and that it began to decrease after 30 years of age. The mean age at the time of the first attack of A.R.F. was 26.6 for the females and 22.2 years for the males. The corresponding ages for group B were 28.4 and

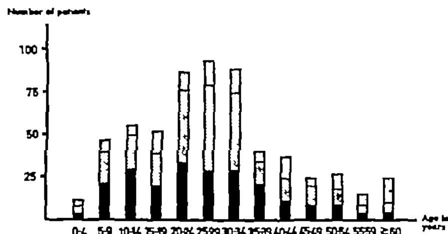


Fig. 8. *Acute polyarthritis*

Classification of females according to age and firmness of diagnosis

Total number of cases 598

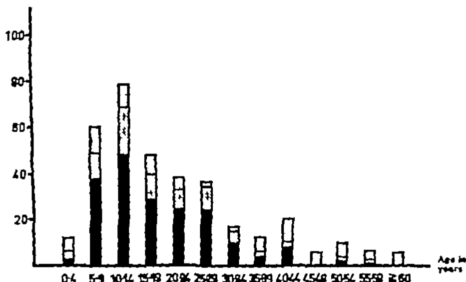


Fig. 12. *Acute endocarditis.*
Classification according to age and firmness of diagnosis.
Total number of cases 350

Firm | Probable | Suspected

Age in years at the first attack in patients with recurrences

Years	0—4	5—9	10—14	15—19	≥20
Number of cases	3	13	10	4	5
Per cent	8.6	37.1	28.6	11.4	14.3

per cent) recurrences and in group C also 3 (3.6 per cent).

In the group with a firm diagnosis of rheumatic fever (group A) the frequency of recurrences did not vary with sex. The mean age at the time of the first attack in patients in the group with recurrences was 13.7 years for the females and 10.6 years for the males.

The second attack occurred in 5 (14.3 per cent) cases within 6—12 months, in 8 (22.9 per cent) during the second year, in 13 (37.1 per cent) within 3—10 years and in 9 (25.7 per cent) after 10 years. The mean age at the time of the second attack was 22.8 years and 17.3 years for females and males, respectively. 18 of the patients had had 3 or more recurrences.

The frequency of recurrences declined during the 25-year period. Of patients in group A admitted because of a first attack of acute endocarditis in 1930—34 8.7 per cent had recurrences, in 1935—39 7.9 per cent, 1940—44 2.4 per cent and in 1945—49 1.8 per cent. None of the patients with their first attack during 1950—54 had a recurrence during this 5-year period.

TRACING OF PATIENTS

On search of the files at the parish offices during the summer of 1958 it was

Age in years at the first attack in patients with recurrences

Years	0—4	5—9	10—14	15—19	≥20
Number of cases	8	27	35	20	27
Per cent	6 8	23 1	29.9	17 1	23.1

females and 8 males). The frequency of recurrences in group A was 21.2 per cent in group B 5 4 per cent and in group C 4 per cent

In females and in males in group A the first attack in patients with recurrences was commonest in the 10—14 year class.

The majority of patients in group B were also below 20 years 9 of 14 females and 0 of 9 males.

Of 151 patients with recurrences 90 had their first attack before 1930 and only 61 during or after this year The firmness of the diagnosis in these 61 patients was as follows. group A 46 or 11 2 per cent group B 10 or 2.4 per cent and group C 5 or 2.2 per cent.

The frequency of recurrences declined during the 25-year period Of the patients in group A admitted because of a first attack of acute polyarthritis in 1930—34 16 5 per cent had recurrences, in 1935—39 13.3 per cent, in 1940—44 8.4 per cent and in 1945—49 4 9 per cent. None of the patients with their first attack during 1950—54 had a recurrence during this 5-year period

ERYTHROCYTE SEDIMENTATION RATE

The erythrocyte sedimentation rate was determined by the microm thod of Landau and by the method of Westergren. The latter method has not changed during the 1930—54 period and since it was used in most of the cases the results obtained by it will be described below

The means of the highest values (mm/1 hr) recorded in the females were 77 2 for 206 in group A, 52.0 for 204 in group B, and 46.8 for 28 in group C. The corresponding figures for the males were 80 9 for 205 in group A, 60 7 for 140 in group B, and 37 1 for 30 in group C. The E.S R did not differ significantly with sex. The difference between group A and B was statistically significant (P < 0 001) but not that between B and C.

Severe cases of A.R.F showed a clear tendency to become less common during the observation period (SELANDER and LJUNGBERG Personal communications) which is in good agreement with the findings of BACH et al. (1939) and WALLGREN (1957). It cannot be excluded that this phenomenon might be reflected in the E.S R. for example The mean values found for the highest E.S.R. recorded within 2 weeks of admission of both sexes are given below for the various 5-year periods.

Erythrocyte sedimentation rate

	Group		
	A	B	C
Number of determinations	411	344	53
1930—34	87 0	60.2	40 0
1935—39	85.5	50.0	42.0
1940—44	7 6	46.9	36.1
1945—49	68.7	49 8	49 5
1950—54	77 0	55 0	41.2

It is clear from the table that there was a decline in the mean E.S R. from 1930 to 1950 when the values again exceeded those noted during the 40ies. The difference between the means for the 30ies differed significantly from that found for the 40ies (P<0.01) for group A but not from that found for the 50ies. A similar though less marked falling tendency of the mean E.S.R. was noted for group B and C in the 40ies.

9 years, 2 between 10 and 14 years and 2 between 20 and 21 years. 5 of these patients are accounted for in the group with acut poly arthritis (cases 3056 1736, 1752, 1750, 1749). The patients (cases 1725 3024) who died t the ge of 20 and 22 years, respectively were not autopsied, and the clinical diagnosis was mitral tenosis with acute endocarditis in the first one and aorti incompetence with cut pericarditis in the second one.

The other 2 patients (cases 3152, 3304) who died at the age of 8 and 9 years, respectively were not aut psied either in one the clinical diagnosis was acut endocarditis; in the other acut endocarditis with involvement of the mitral and tricuspid valves. In the 2 patients (cases 1619 1630) who died during an ttack of A.R.F., death occurred at the ges of 43 and 41 years, respectively At autopsy the former showed aortic stenosis with an acut endocarditis of the mitral and aortic valves, while the other had clinical diagnosis of chronic endocarditis with recurrence. The age of the patients at the time of the first attack had not been noted in their record sheets.

Of the 85 females in group A and of the 108 males 8 and 3 (9 4 and 2.9 per cent) respectively died. The difference is almost significant ($P<0.05$)

In group B — probable rheumatic fever — 6 (8 2 per cent) patients had died and 4 during the acute phase of the disease

2 patients, (cases 2995, 3030) both males, died at the age of 25 and 26 years in 1930 and 1940, and autopsy showed ortic and mitral lesions and bacterial endocarditis in both. On female (case 1673) ged 3., was moribund on admission to hospital, and autopsy showed M.S.M.I. and heart failure, but no signs of acute endocarditis. The last patient, woman (case 1537) ged 54 had had 4 uncharacteristic attacks of rheumatic fever t the ages of 17 39, 48 and 54 and autopsy showed mitral tenosis, cut endocarditis and hemorrhagi pericarditis.

In group C — suspected rheumatic fever — 35 (41 7 per cent) had died, and 16 (19 1 per cent) during the acute phase of the disease.

4 patients had bacterial endocarditis at autopsy and in 8 cases this diagnosis was suspected on clinical grounds. In 1 case, (case 3060) 4-year old boy autopsy showed perimyocarditis, but valvular lesions and no Aschoff granulomas; in another one (case 1604) 63-year old woman, pleurisy and pericarditis, but no signs of A.R.F either

In 2 girls, (cases 1837 3329) aged 2 and 6 years and not autopsied, the clinical diagnosis was acute pericarditis and acut endocarditis in one and acute polyarthritis and acut endocarditis as well as epidemic hepatitis in the ther

RESULTS OF THE RE-EXAMINATION IN 1953 OR LATER

150 patients were re-examined either in 1953 or in the 1955—58 period representing 40 4 per cent of the entire material (371 cases) and 57.3 per cent of these who were still alive or who could be traced in 1958. The frequency of R H.D in the re-examined series was 26 0 per cent while 52.7 per cent were judged as not having heart disease. The uncertain R.H.D contained 21.3 per cent which could not be classi fied as normal because of auscultatory electrocardiographic and/or roentgen find ings.

RESULTS OF RE-EXAMINATION OF PA TIENTS CLASSIFIED ACCORDING TO FIRMNESS OF DIAGNOSIS

RHEUMATIC HEART DISEASE, CERTAIN

Table 10 shows that within group A — firm diagnosis — the distribution of certain R.H.D among females and males was 32.5 per cent and 27.8 per cent. The difference was not significant. The obser vation period varied from 4 to 52 years and the number of person years was 1,252, calculated from the first attack of rheu matic fever

In group B — the frequency of R.H D was 0.0 per cent and 17 4 per cent for females and males, respectively The observation period varied from 3 to 51 years and the number of person years was 410 as calculated from the first attack of rheumatic fever

In the suspected group — group C — R.H.D was found in 7 of 21 patients examined.

These noteworthy findings deserve commentation. Of the 6 females, 2 had had one suspected ttack of A.R.F before 1930, 2 severe tonsillitis only (but clinically suspected A.R.F because of concomitant elevation of E.S.R.), and in 2 A.R.F had been suspected during 1930—54. One f

Table 4. Survey of acute polyarthritis series.
Females.

	1930—34	1935—39	1940—44	1945—49	1950—54	Total
	119	118	166	168	113	684
Group A	66 (55.5)	47 (39.8)	7 (31.3)	47 (28.0)	35 (31.0)	252 (36.8)
Group B	34 (28.6)	41 (34.7)	67 (40.4)	73 (43.5)	43 (38.1)	258 (37.7)
Group C	11 (9.2)	20 (16.9)	34 (20.5)	36 (21.4)	31 (27.4)	132 (19.3)
No clinical data	8 (6.7)	10 (8.5)	8 (4.8)	12 (7.1)	4 (3.5)	42 (6.1)
Follow-up 1955						
Deaths	17 (14.3)	12 (10.2)	10 (6.0)	9 (5.4)	6 (5.3)	54 (7.9)
Not traced	18 (15.1)	1 (14.4)	16 (9.6)	3 (1.8)	3 (2.7)	57 (8.3)
Survivors						
Examined	37 (31.1)	49 (41.5)	79 (47.6)	99 (58.9)	45 (39.8)	309 (45.1)
Not examined	47 (39.5)	40 (33.9)	61 (36.7)	57 (33.9)	59 (52.2)	264 (38.6)

(Figures in brackets indicate percentages)

Table 5. Survey of acute polyarthritis series.
Males.

	1930—34	1935—39	1940—44	1945—49	1950—54	Total
	101	92	138	94	99	524
Group A	55 (54.5)	42 (45.7)	62 (44.9)	34 (36.2)	38 (38.4)	231 (44.1)
Group B	29 (28.7)	37 (40.2)	41 (29.7)	33 (35.1)	30 (30.3)	170 (32.4)
Group C	15 (14.9)	7 (7.6)	31 (22.5)	23 (24.5)	27 (27.3)	103 (19.7)
No clinical data	2 (2.0)	6 (6.5)	4 (2.9)	4 (4.3)	4 (4.0)	20 (3.8)
Follow-up 1955						
Deaths	12 (11.9)	11 (12.0)	11 (8.0)	7 (7.4)	1 (1.0)	42 (8.0)
Not traced	18 (17.8)	13 (14.1)	11 (8.0)	7 (7.4)	2 (2.0)	51 (9.7)
Survivors						
Examined	32 (31.7)	47 (51.1)	81 (58.7)	57 (60.6)	36 (36.4)	253 (48.3)
Not examined	39 (38.6)	21 (22.8)	35 (25.4)	23 (24.5)	60 (60.6)	178 (34.0)

(Figures in brackets indicate percentages)

(15.7 per cent) had died and 8 (3.4 per cent) during the acute phase of the disease.

Of these patients 1 (case 1061) proved to be Morbus Little, 1 (case 3329) epidemic hepatitis, 2 (cases 441, 3068) acute myocarditis, 1 (case 2923) septicemia on the basis of pneumonia and 1 (case 1501) pleurisy with pericarditis. The remaining 2 (cases 7124, 3025) patients, who died at the age of 17 and 37, will be described in greater detail.

Case 7124. The patient was a 17 year old male, who had had scarlet fever at 6 years, but who had otherwise always been well until 16, when anaemia and aortic incompetence were diagnosed. He had had no recent respiratory tract infection and no joint pain. On admission he was cyanotic, and dyspnoeic with signs of severe congestion. A loud diastolic murmur with punctum maximum over the left I_{3-4} was heard as well as a systolic murmur over the apex. Roentgen examination of the heart showed a relative volume of 830 cc/m² body surface with enlargement, particularly of the left ventricle, but also of the left atrium. Standard electrocardiogram showed normal axis, sinus rhythm and no definite signs

mal t the review in 1953, the diagnosis was only uncertain R.H.D

In the group with a firm diagnosis of A.R.F., 35.0 per cent and 51 9 per cent of the females and males respectively the diagnosis of R.H.D was excluded. The difference between the sexes was not significant.

C. CHOREA MINOR

Analysis of the files of Malmö General Hospital for the years 1930—54 revealed a total of 100 first admissions with a diagnosis of chorea minor The distribution of the cases among 5-year periods is given in Fig. 13. 14 cases (14 0 per cent) had a diagnosis with a question-mark on first admission. It is clear from the histogram that the number of cases decreased during the 30ies but then showed a considerable increase during World War II. After 1945 the number of new cases decreased rapidly and no new cases were notified after 1952. The number of cases notified in 1930—34 and 1935—39 were 32 and 19 respectively while during the 1940—44 45—49 and 50—54 periods 32 12 and 5 cases were notified. It would of course be better if the patients with chorea minor be classified according to the firmness of the dia gnosis but this was not possible Therefore those cases in which the diagnosis was without a question mark were assigned to group A and those with to group B The frequencies of the cases in group A in the 5-year periods were 29 18 27 9 3. The increase during the War was significant ($P<0.01$) The most common dia gnoses made in association with the dia gnosis of chorea minor were acute endocarditis and rheumatic heart disease.

Of 86 cases with a firm diagnosis 15 (17 4 per cent) also had acute endocarditis and the number of cases in the 5-year groups were 27 6—5 6—18.5—11 1—0.0 per cent. The frequency thus declined during the period covered by the present investigation except for the years of the

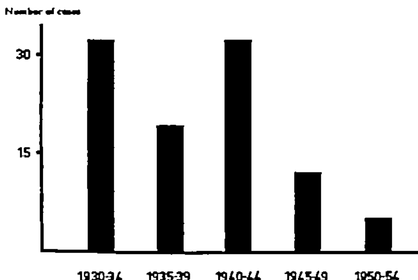


Fig. 13. *Chorea minor*
Total number f cases 100.
(Females 62, males 38)

Table 6. Acute polyarthritis.
Result of the re-examination.

Firmness of the diagnosis	Sex	Rheumatic heart disease			Total
		Certain	Uncertain	Excluded	
Firm	♀	31 (22.5)	21 (15.2)	86 (62.3)	138
	♂	22 (16.8)	19 (14.5)	90 (68.7)	131
Probable	♀	8 (6.1)	21 (16.0)	102 (77.9)	131
		7 (8.2)	9 (10.6)	69 (81.2)	85
Suspected		1 (2.5)	7 (17.5)	32 (80.0)	40
		0	3 (8.1)	34 (91.9)	37

(Figures in brackets indicate percentages)

no audible murmur. Lab data: E.S.R. 24 24 mm 1 hr. AST 900 and 320 I.

At re-examination at 14 years of age the patient felt well, but auscultation revealed a systolic murmur grade II—III in left third intercostal space and a diastolic murmur indicating aortic incompetence. Normal heart sounds and normal blood pressure.

Electrocardiography on admission and on re-examination showed no abnormalities. X-ray showed a relative heart volume of 280 cc m² body surface and normal configuration except slight bulge at the site of the left atrium in the lateral view.

RHEUMATIC HEART DISEASE, UNCERTAIN

The group with the firm diagnosis of A.R.F. — group A — contained 40 patients, i.e. 14.9 per cent uncertain R.H.D., of whom 21 were females (15. per cent) and 19 males (14.5 per cent).

10 females and 3 males were regarded as uncertain R.H.D. because of auscultatory and roentgen findings, 3 females and 3 males because of auscultatory and 8 females and 13 males because of roentgen findings only. In roentgenologically suspected cardiac disease the suspicion was due to a posterior bulge at the site of the left atrium as well as slight enlargement of the left ventricle in 7. The relative heart volume was slightly increased in 3.

females and 5 males in this group were re-examined 4—6 years after the first examination. One woman classified under uncertain R.H.D. because of auscultatory and roentgen findings was found to have aortic incompetence with slight enlargement of the heart. In 4 women who were classified as uncertain R.H.D. because of slight bulge of the left atrium only, the re-examination revealed no roentgen signs or other evidence of a pathologic condition. 2 women were classified as uncertain R.H.D. because of auscultatory findings. In one of the cases there was a systolic murmur of grade III along the left sternal edge, but otherwise the examination revealed nothing of interest and in the other case there was a loud first sound over the apex and a systolic (but not pan-systolic) murmur and split second sound, but the roentgenogram and the electrocardiogram were normal.

Of 8 men with a slight bulge of the left atrium, 7 showed no roentgen abnormalities at this re-examination, while in 1 case the left atrium bulged posteriorly although auscultation revealed nothing suggestive of R.H.D. Of 2 cases described as uncertain R.H.D. because of auscultatory findings, one could be dismissed, while the other was kept under observation because of an apical systolic murmur grade III (not pan-systolic).

In group B uncertain R.H.D. was present in 30 out of 216 patients examined, i.e. 14.0 per cent. There were 21 females (16.0 per cent) and 9 males (10.6 per cent).

Uncertain R.H.D. because of auscultatory findings included 4 females but no males. Uncertain auscultatory findings were more common in females than in males with a firm or

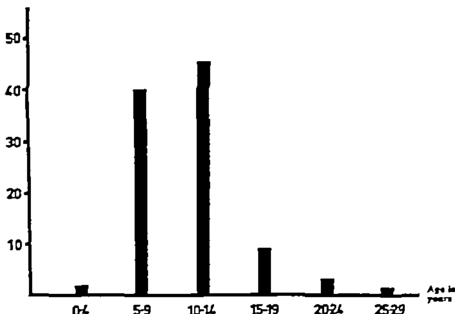


Fig. 14. *Chorea minor*

Age distribution.

patients could not attend the review because they had moved out of town, 3 of them abroad. Of the remaining 82 patients, who were residents of Malmö 78 (95.1 per cent) were reviewed. 4 patients, all males, were living far from Malmö and were not able to attend the review but all of them reported that they felt well. The reason why attempts were made to examine as many of the patients in this group as possible was that the author wished to show by means of a representative sample whether the material described was biased or not (see p. 14).

MORTALITY

Of a total of 100 patients, 95 could be traced and 8 of them had died in the meantim e. 8.4 per cent. 4 patients had died from the first attack of rheumatic fever had died in hospital and 3 of them had been aut psied.

Case 1 43 A 16-year old girl with chorea at the age 1 and recurrences at 6 and 1 years. She had had no other manifestation of rheumatic fever. During her stay in hospital the E.S.R. was less than 4 mm/1 hr. At 16 years of ag tuberculosis of the hilus and tuberculous meningitis occurred, and the girl died. Post mortem examination showed in addition to tuberculous changes slight enlargement of the heart, and the mitral valve was almost normal, but the valves were nodular and thickened. The other ostia and valves were of normal ppearance

Case 1752. A 6-year old girl who had had short bout of joint symptoms localised t the hands and knees for which she had not been admitted to hospital. 3 months later she was, however dmitted because of slowly progressing symptoms of chorea. On admission she was in poor condition with signs of pericarditis and endocarditis. 1 week later she developed an infection of the upper respiratory tract, which was complicated by scarlet fever. 5 weeks later the patient died from heart failure. Post mortem examination revealed a markedly enlarged heart with fibrinoid adhesions in the pericardium. The endocardium showed no gross changes. Microscopic examination showed numerous Aschoff granulomas in the myocardium but nothing is said about changes in the endocardium.

Case 3304 A 9-year old boy with chorea and cute endocarditis, which proved fatal within 4 weeks despit intense salicylic acid therapy. Post-mortem examination revealed enlargement

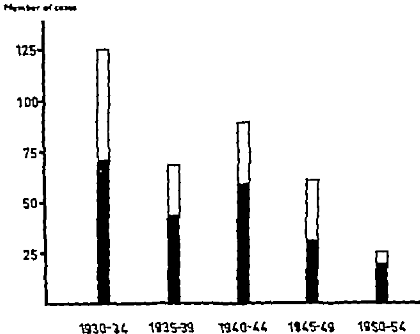


Fig 10. *Frequency of acute polyarthritis patients with diagnosis of acute endocarditis.*

Acut endocarditis — Acute polyarthritis and acute endocarditis

the beginning to the end of the period covered by the investigation was from 2.0 per 10,000 inhabitants per year to 0.3. The increase during the years f the War still persisted but it was no longer so striking, but significant.

CORRECTION FOR PATIENTS WITH FIRST ATTACK BEFORE 1930

Of 371 patients with acute endocarditis during th 1930—54 period hospital records containing satisfactory data were available in 350 (94.3 per cent). Of these 350 patients, 21 (6.0 per cent) had had their first attack bef re 1930: 15 of them were hospitalised in the 1930—34 period 2 in the 1935—39 period 3 in the 1940—44 period and 1 in the 1945—49 period. The frequency of a diagnosis of acute endocarditis f r patients who had had their first attack during or after 1930 was: 103 63 82 56 and 25 per 5-year period.

FREQUENCY OF THE DIAGNOSIS OF ACUTE ENDOCARDITIS CLASSIFIED ACCORDING TO THE FIRMNESS OF THE DIAGNOSIS

The hospital records were available in 350 (94.3 per cent) of a total of 371 cases, and the firmness of the diagnosis was based on data from these records. The cases were grouped according to th classification described in the chapter on Definiti ns (see p 10).

Group A — firm diagnosis of rheumatic fev r — contained 193 (55 1 per cent) patients group B — probable diagnosis — 73 (20 9 per cent) and group C — suspected — 84 (24 0 per cent)

The distribution is given diagrammati cally in Fig. 11 The numbers of cases in group A in the respective 5-year periods were: 73 31 55 18 and 16 the corresponding figures for group B being 20 16, 14 20 and 3 and for group C 23 18, 17 19 and 5 It is obvious that the increase

examiners could not decide with certainty whether mitral incompetence was present or not. All murmurs were of grade III, and none were heard in the left axilla.

The cases regarded as uncertain because of roentgen findings consisted of 8 patients (6 females and 2 males) with a bulgent left trium and the possibility of valvular disease was meagre (HALL et al. 1961).

1 patient was f und to ha e a cerebral injury probably sustained during delivery which per sisted and caused severe symptoms of chorea-lik appearance when the patient was 23.

Table 7 Classification of females nd males according t ge and firmness of the diagnosis of acut endocarditis.

Age in years	Group A		Group B		Group C	
	F	M	F	M	F	M
0—4	1— 1 2	2— 1 9	1— 3.3	2— 4 7	2— 4 0	3— 8.8
5—9	16— 18 8	21—19 4	5—16.7	6— 14 0	6— 12 0	6—17 6
10—14	21— 24 7	28—23.9	4—13.3	16— 37.2	3— 6.0	7—20.6
15—19	12— 14 1	17—15 7	4—13 3	6— 14.0	6— 12 0	3— 8.8
20—24	12— 14 1	13—12 0	4—13.3	4— 9.3	3— 6 0	2— 5.9
25—29	12 14 1	13—12 0	3—10 0	7— 16.3	2— 4.0	0
30—34	3— 3.5	7— 6 5	5—16.7	0	2— 4.0	0
35—39	1— 1 2	3— 2 8	1— 3 3	1— 2.3	5— 10.0	1— 2 9
40—44	5 5 9	3— 2 8	1— 3.3	1— 2.3	3— 6.0	—20 6
45—49	0	0	0	0	4— 8.0	2— 5.9
50—54	1 1 2	1— 0 9	1— 3.3	0	5— 10 0	2— 5.9
55—59	1— 1 2	0	1— 3.3	0	4— 8 0	0
≥60	0	0	0	0	5— 10,0	1— 2.9
T tal	85— 100 0	108—99 9	30—99 8	43—100,1	50—100 0	34—99 9

group B (30 females 43 males) *i.e.* a quotient of 1/1 3 and 1 1 4 respectively The sex difference was not significant If correction is made f r sex and age in the population

In group C there were 50 females and 34 males.

The sex distribution per 5-year period showed the f llowing ratio (females/ males) 1930—34 1/1.2, 1935—39 1/1.0 1940—44 1/1 6, 1945—49 1/0 8 and 1950 —54 1/3.8 for all cases and for group A per 5-year period 1/1 2, 1/1 1 1/2.2, 1/1 0 and 1/3.0 respectively

AGE DISTRIBUTION

Fig. 12 shows the ages at the time of the first attack in 350 cases, whose histories were known. In group A the frequency showed a peak between the ages of 10—14 years, and the average at the time of the first attack was 17 2 years. For group B the peak was also noted between 10—14 years, and the average age at the time of the first attack was 15.6 years. Group C showed no peak and the mean age at the time f the first attack was 29.5 years.

The age distribution of either sex according to firmness of diagnosis is given in Table 7 20 0 per cent of the females and 21.3 per cent of the males had had had their first attack before 10 years, 38 8 per cent and 41 7 per cent respectively between 10—19 years; 28.2 per cent and 24 1 per cent respectively between 20—29 years, and 12.9 per cent and 13.0 per cent respectively after 30 years of age. In group B 46 7 per cent of the females and 69.8 per cent f the males had had their first attack below the age of 20 years. In both of these groups there was a tendency of the peak between 10—14 years to be more marked for males than for females. In group C there was no marked peak and the cases were fairly evenly distributed over the age scale

FREQUENCY OF RECURRENCES

As in the classification of recurrences of acute polyarthritis, a recurrence of acute endocarditis was said to be present if the attack had been preceded by a symptom free remission of at least 6 months with a normal E.S.R. Of 350 cases in whom the history was known 41 (11 7 per cent) had had one or more recurrences up to 1955. In group A, 35 (18.1 per cent) had recurrences In group B there were only 3 (4 1

Electrocardiography and roentgen examination of the heart have been used throughout the period, though only to a limited extent in the beginning The majority of the patients with A.R.F had been examined electrocardiographically and roentgenographically on at least one occasion in the beginning of the period as against several occasions towards the end of the period.

A retrospective investigation of any material not initially intended for scientific analysis must have its limitations. On the other hand, the only possibility available today to judge the changes in the panorama of the disease and in its natural history is to analyse data available in the hospital records and from the information thereby obtained of the past try to widen our knowledge and possibly predict the future. The advantage of the present material is that it has been collected from a well defined population.

FIRM RHEUMATIC FEVER ACCORDING TO JONES MODIFIED CRITERIA

On analysis of the material it proved necessary to grade the diagnoses according to firmness in accordance with the scheme described in the chapter on Definitions This classification was made without knowledge of the findings at later examinations or at autopsy

A firm diagnosis of acute rheumatic fever according to Jones criteria was regarded as justified in 588 patients or 41 0 per cent. Clinical diagnosis of acute polyarthritis + acute endocarditis + chorea minor was made in 3 patients acute polyarthritis + acute endocarditis in 154 acute polyarthritis + chorea minor in only 1 acute endocarditis + chorea minor in 15 acute endocarditis only in 23 chorea minor only in 67 and acute polyarthritis only in 325 The other major manifestions in the form of erythema marginatum and sub-

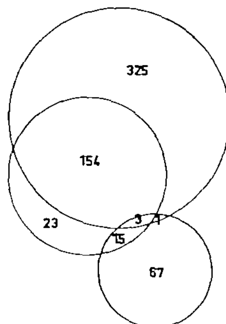


Fig. 15. Distribution diagram of patients with firm diagnosis of cut rheumatic fever

Table 8. Survey of acute endocarditis series.
Females.

	1930—34	1935—39	1940—44	1945—49	1950—54	Total
	70	33	36	33	5	177
Group A	39 (55.7)	16 (48.4)	17 (47.2)	9 (27.3)	4 (80.0)	85 (48.0)
Group B	12 (17.1)	4 (12.1)	4 (11.1)	10 (30.3)	—	30 (16.9)
Group C	12 (17.1)	12 (36.4)	12 (33.3)	13 (39.4)	1 (20.0)	50 (28.2)
No clinical data	7 (10.0)	1 (3.0)	3 (8.3)	1 (3.0)	—	12 (6.8)
Follow-up 1955						
Deaths	18 (25.7)	11 (33.3)	7 (19.4)	8 (21.2)	1 (20.0)	45 (25.4)
Not traced	9 (12.0)	2 (6.1)	3 (8.3)	2 (6.1)	—	16 (9.0)
Survivors						
Examined	16 (22.9)	11 (33.3)	18 (50.0)	16 (48.5)	2 (40.0)	63 (35.6)
Not examined	27 (38.6)	9 (27.3)	8 (22.2)	7 (21.2)	2 (40.0)	53 (29.9)

(Figures in brackets indicate percentages)

Table 9. Survey of acute endocarditis.
Males.

	1930—34	1935—39	1940—44	1945—49	1950—54	Total
	56	36	54	28	20	194
Group A	34 (60.7)	15 (41.7)	38 (70.4)	9 (32.1)	12 (60.0)	108 (55.7)
Group B	8 (14.3)	12 (33.3)	10 (18.5)	10 (35.7)	3 (15.0)	43 (22.1)
Group C	13 (23.2)	6 (16.7)	5 (9.3)	6 (21.4)	4 (20.0)	34 (17.5)
No clinical data	1 (1.8)	3 (8.3)	1 (1.9)	3 (10.7)	1 (5.0)	9 (4.6)
Follow-up 1955						
Deaths	10 (17.9)	6 (16.7)	8 (14.8)	1 (3.6)	1 (5.0)	26 (13.4)
Not traced	*8 (14.3)*	*8 (22.2)*	*3 (5.6)*	*2 (7.1)*	*1 (5.0)*	*22 (11.3)*
Survivors						
Examined	17 (30.4)	13 (36.1)	31 (57.4)	18 (64.3)	8 (40.0)	87 (44.8)
Not examined	21 (37.5)	9 (25.0)	12 (22.2)	7 (25.0)	10 (50.0)	59 (30.4)

(Figures in brackets indicate percentages)

possible to ascertain how many of the patients were still alive on January 1 1958. 38 (10.2 per cent) patients could not be traced mainly because of lack of primary data, and 71 patients (19.1 per cent) had died. Of the remaining 262 patients, 150 (57.3 per cent) were reviewed in 1953 or later (Tables 8 and 9)

MORTALITY

Of the 61 patients 48 had died in hospital and 29 of them had been autopsied. 13 patients had died outside the hospital departments studied.

Of 193 patients with a firm diagnosis of rheumatic fever 20 (10.4 per cent) had died 11 (5.7 per cent) of them during an acute attack.

The mortality during the acute phase decreased during the 25-year period covered by the investigation. The numbers of deaths for the respective 5-year periods were: 6 2, 2, 1 and 0

Of these 11 patients, 9 died during the first attack. 1 at the [illegible] of 4 years, 4 between 5 and

of 17 years at the time of their first attack, while patients with acute polyarthritis had their first attack at a mean age of 25 years. The age distribution shows two peaks one between 10—14 years and one between 20—29 years. The age distribu tion of A.R.F is intimately related to the spread of streptococci in the population and thus CONUBN (1944) and others found a very high frequency of A.R.F in mili tary camps. It is therefore tempting to assume that the increased frequency in the 20—29 year group might be due to the males having been called out for military service and to the females and males hav ing children in school Both factors imply a greater exposure to streptococci. A.R F in the present material tended to be somewhat more common among females with their first attack between 20—29 and with children at home than among females without children.

The mean age at the time of the second attack in the present material was 26 years and another possible explanation of this second peak might be that the first attack was never more than subclinical and that what was registered as the first attack was in reality the second or third. Careful analysis of the clinical series however yielded no evidence in favour of this assumption

FREQUENCY OF RECURRENCES

The patient was said to have a recur rence of rheumatic fever if in the mean time he had been symptom-free for 6 months and the E.S.R. had been normal during that time. Recurrences occurred in 24 per cent of the group with a firm diagnosis of acute polyarthritis and in 16 per cent of the group with a firm diagnosis of acute endocarditis. Almost 80 per cent of the patients with recurrences had their first attack before 20 years of age usually between 10—14 years and no patient without signs of chronic cardiac involvement above 30 years of age at the time of the first attack in group A had recurrences. The declining frequency of recur rences in higher age groups was also observed by EDSTRÖM (1935) who could show a recurrence frequency of 50 per cent in his material which may in some measure be due to the different definition of the term "recurrence but also to a decreasing tendency of recurrences which had been shown by WILSON et al. (1958) and others.

The frequency of recurrences declined during the 25-year period, and none of the patients with their first attack during 1950—54 had a recurrence. This reduction in the frequency of recurrences can be ascribed in part to decreasing duration of follow up but since 40 per cent of the recurrences occurred within 2 years of the first attack and 80 per cent within 10 years it would appear that the frequency of recurrences must have decreased.

The American recommendation of peni cillin prophylaxis is based on the high frequency of recurrences and on the pronounced tendency of R.H.D to develop in patients with recurrences. Since 80 per cent of the recurrences were noted in patients who had had their first attack before the age of 20 years this group in particular should receive prophylaxis (as far as Sweden is concerned) and it is clear from the data given that such prophylaxis should be continued for several years. On the other hand in patients above 30 years without signs of R H D (certain or uncer tain) routine prophylaxis is not necessary

The above considerations should be borne in mind in the discussion of the range of indications for prophylaxis.

MORTALITY

The mortality during the acute phase of rheumatic fever in the present material which continously decreased was for the entire group with a firm diagnosis 2.0 per cent. This is in agreement with the figure given by GRASER (1960).

Late deaths occurred from 3—28 years for the entire group in 6.1 per cent. ARRSO et al. (1951) reported a somewhat higher

Table 10. Acut endocarditis.
Results f the re-examination

Firmness f the diagnosis	Sex	Rheumatic heart disease			Total
		Certain	Uncertain	Excluded	
Firm	♀	13 (32 5)	13 (32.5)	14 (35.0)	40
	♂	15 (27.8)	11 (20 4)	28 (51 9)	54
Probable	♀	0	3 (25.0)	9 (75.0)	12
		4 (17 4)	4 (17 4)	15 (65 2)	23
Suspected		6 (54 5)	0	5 (45.5)	11
		1 (10 0)	1 (10 0)	8 (80 0)	10

(Figures in bracket indicat percentages)

the patient had had scarlatina t 18 years, when th clinicia had suspected endocarditis but found no signs of A R F At 37 years the patient was found t ha A.I and M S M I The other patient had had pericarditi t 10 years and an elev ted E.S.R., but had sho no other signs On xamination during the 50ies, the patient had had constant murmur indicati g aortic incompetence.

RHEUMATIC HEART DISEASE, UNCERTAIN

In the group with a firm diagnosis of rheu matic fever — group A — 32.5 per cent of the f males nd 20 4 per cent f the males had uncertain R.H D

Of 13 f males in this group the condition had been suspected, i 7 because of auscultatory and roentgen findings, i 1 case because of uscultatory findings only and in 5 because of roentgen findings only Of the first mentioned patients, 5 had slight backward bulge at the site of the left trium in lateral views, 2 had certain en largement and 2 also slightly enlarged left ventricle I all the cases the relative heart olume was normal The auscultatory findings consisted of ystolic murmur over the apex or left I_{4-} f grad III In 1 case signs of A.S A.I. superv ened later and in another M.S. while the auscultatory findings in the remainder persisted unchanged

The patient with uncertai R.H D on auscultatory grounds only was 71 year old woman who t first examination had had an inconstant diastolic murmur er left I_3. Re-examination revealed that the murmur was constant, but the blood pressure electrocardiogram and roentgen xamination howed no abnormalities.

The 5 cases, i which re-examination w considered desirable because of roentgen findings only were made the subject of special investigation, on which it was found that bulgent left trium in lateral views is by no mea strong evidence of R H.D (HALL et al. 1961).

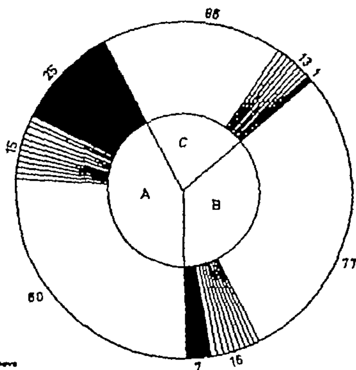
In none of the males has it been possible to make a firm diagnosis f R.H.D

In the group with probable A.R.F 25 0 per cent of the females and 17 4 pe cent f the males had uncertain R H.D., re spectively

One of the patients, 50-year old woman, had had systolic murmur grade III over the pex but had no roentgenographic or lectrocardiographi abnormalities, and re-examination had yielded evidence suggesti of M I. In none of the other patients in this group has it been possible t mak firm diagnosis of R.H.D

Finally in group C — suspected A.R.F — there was only 1 case of uncertai R H.D

The patient was 60-year old man with systolic murmur grade III in the left I_{3-4}, and roentgenography had shown left entricular en largement, and electrocardiography showed left xis deviation but no certain signs of left ventri cular hypertrophy Since the blood pressure had been elevated t previous examinations but ner

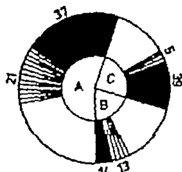


Circles from above

Acute polyarthritis
(number of cases 1 146—A 42, B 37 and C 21 per cent)

Acute endocarditis
(number of cases 150—A 55, B 21 and C 24 per cent)

Chorea minor
(number of cases 100—A 86, and B 14 per cent)



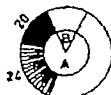


Fig. 16. Group A — firm diagnosis of acute rheumatic fever. Group B — probable diagnosis of acute rheumatic fever. Group C — suspected diagnosis of acute rheumatic fever. Filled areas: Rheumatic heart disease certain. Hatched areas: Rheumatic heart disease, uncertain. Blank areas: Rheumatic heart disease, excluded.

War In 15 (1 4 per cent) cases the patients had had not only chorea minor but also chronic R.H D In 12 cases it had not been n ted which valve was involved and 3 had mitral lesions. The frequency of valvular disease also declined (2 6—16. — 4—22.2—0 per cent) with the exception of the years 1945—49 but the increase noted then was n t statistically significant. 8 patients had R.H.D without acute endocarditis while also had endocarditis. *In only 4 was ch rea minor associated* with acut poly rthritis 2 admitted in the 1930—34 period and 2 in the 1940—44 period. In none of the cases in group B did the patients show signs of polyarthritis endocarditis r R.H D

CORRECTION FOR PATIENTS WITH FIRST ATTACK BEFORE 1930

Data were available on all of the 100 patients. Only in 1 case a girl — had th first attack of chorea minor occurred bef re 1930. The girl had had her first attack t the age of 5 in 1926 and a recurrence in 1931 The number of patients with the first attack before 1930 thus has no effect on conclusions that might be drawn from analysis of th material dating from the 1930—54 period.

SEX DISTRIBUTION

The ratio of females t males in the above-mentioned series of 100 patients was 1 6/1 (62 females and 38 males). The corresponding ratio f r group A was 1.9/1 (56 females and 30 males) and the difference was significant ($P < 0.001$).

AGE DISTRIBUTION

The age distribution of th material at the time f first admission during 1930—54 is given in Fig. 14. It is clear that 85 per cent had had their first attack at 5—15 years of age (40 at 5—9 years and 45 at 10—14 years). Only 2 patients were below 5 years 9 between 15—19 and 4 were 20 years or more. The 4 last mentioned patients had had chorea during school age and none had the first attack after 20 years of age The numbers of cases in group A in the various age groups were 2, 37 40 7 (average 9 7) The age at the time of onset did not vary with sex. Of the 14 patients in group B 5 had had th first attack at 5—9 7 at 10—14 and 2 at 15—19 years of age

FREQUENCY OF RECURRENCES

In the present investig tion a recurrence was said to have occurred if th symptoms had been considered severe enough to indicate admission to hospital. The course of the chorea was judged according to the number of re-admissions. None of the patients in group B had been re-admitted because of recurrent symptoms as against 15 (17 4 per cent) of those in group A. Recurrences were observed in 13 females and 2 males (23.2 and 6 7 per cent). The females had been re-admitted n a total of 24 occasions (6 during the lst year during the 2nd 6 during the 3rd to 5th years and 5 more than 5 years after the first admission) In 4 of the 13 patients of this group with recurrent chorea chorea had been accompanied by acute poly arthritis in 1 and more than 5 years after the first attack 3 patients had polyarthritis as the only sign of rheumatic fever *None of the males had been re-admitted* because of chorea, and in 2 acute poly arthritis had been diagnosed 2 years and 8 years respectively after the onset f chorea.

The frequency of recurrent rheumatic fever in the form of acut polyarthritis did not vary with sex.

TRACING OF PATIENTS

On search of the files at the parish offices in 1958 it was possible to ascertain how many of the patients were still alive n January 1., 1958. 5 (5 per cent) patients could not be traced, mainly because of lack of primary data and 8 had died. 5

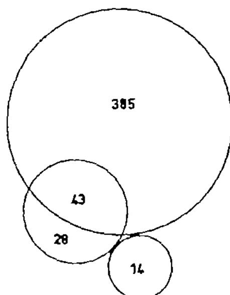


Fig. 17 Distribution diagram of the patient with probable diagnosis of acut rheumatic fever

polyarthritis in 385 (81 9 per cent) and chorea minor in 14 (3.0 per cent) Fig. 17

The diagnosis of probable rheumatic fever was most common during the period 1940—44 In addition there was a tendency for females to be predominant throughout the entire period covered by the investigation, but this tendency was significant only during World War II and in 1945—49 The frequency per 10 000 inhabitants was: 1 2—1 2—1.3—1 2 and 0 7

It is obvious that, even if the manifestations of a disease satisfy Jones modified criteria it is not absolutely certain that the disease is rheumatic fever In this group in which there was no agreement and in which the sex distribution suggested that not all of the cases were instances of rheumatic fever other diseases must be considered, such as rheumatoid arthritis lupus erythematosus disseminatus (L.E.D) sarcoidosis erythema nodosum postinfectious rheumatism etc. It should however be remembered that with our present knowledge of rheumatic diseases it may not be possible to classify more than 1 out of 8 patient (Conn et al. 1955).

At the re-examination less than 1 per cent of the group with a firm diagnosis of rheumatic fever had signs of rheumatoid arthritis against 3.2 per cent in the group with probable A.R F Rheumatoid arthritis can therefore hardly be held responsible for the difference in the sex distribution during the 40ies.

Neither was there any reason to assume that the difference in the sex distribution was due to L.E.D

Erythema nodosum was noted in 51 out of 1,208 patients with acute polyarthritis. This group consisted of 45 females and 6 males and most of th patients were between 20 and 34 years old. In group A erythema nodosum occurred in 9 cases; in group B in 37 and in group C in 3 cases (in 2 cases the notes in the records were incomplete). Only 4 of these 51 patients had tuberculosis of the lungs. Of a total of 51 patients 23 have been re-examined, and none has shown signs of R.H.D A total of 120 patients with erythema nodosum admitted during 1930—50 were re-examined in 1953 and only one was found to have R H D (Björck 1955) The risk of R.H D developing in

of the heart d hanges in the form of thickening, and nodules in the mitral d tricuspid valves.

2 patient died in hospital but were not autopsied. One (case 3506) was an 8-year ld boy who had horea and acut endocarditi following acut tonsilliti and in whom sepsi was regarded as the cause of death. The other (case 1788) was 11 yea ld girl in whom the diagnosi was chorea only The cause f death is not known.

Of the 3 patient who died outside the hospital departments tudied, 2—1 female and 1 male — had probably died from complications f an acquired valvular disease t the age of 31 and 37 years, respecti ly In both cases the diagnosi f R.H.D had been made in association with the first ttack of chorea. The third patient had probably not h d horea but cerebral tumou

The acute mortality in the patients with a firm diagnosis was 4.7 per cent but no deaths have been reported in association with chorea since 1941 Late deaths occurred in (4 7 per cent) during the years 1930 to the end f 1957 f — 2,648 person years. None f the patients in group B h ve died.

RESULTS OF RE-EXAMINATION IN 1953 OR LATER

78 patients were examined. 8 cases had the diagnosis of chorea minor with question-mark and in all of them — 4 females nd 4 males — examination of the heart had revealed no abnormalities. The remaining 70 cases are accounted for in Table 11 The frequency of certain R.H D was 18.6 per cent uncertain R.H D 24.3 per cent The frequency of rheumatic heart disease did not vary significantly with sex.

The diagnosis of uncertain R.H.D was made in 3 because of auscultatory and roentgen findings in 6 — all females — because of auscultatory findings and in 8 because of roentgen findings.

In 3 cases — all females — there wa not only bulging left atrium but also apical *systolic murmur* 1 patient had horea t 9 years of age which was complicated by alvula disease and she was exempted from gymnastics throughout school-time. On examination t 32 years she had an pical systolic murmur of grade III with normal first and split second sound but no murmur in diastole Roentgen examination showed normal sized heart with slightly bulgent trium and enlarged entricle Since the systolic murmur was not audible in the left axilla and since it was not pan-systolic (phonocardiogram) with certainty the di gnosis was uncertain R.H.D

In the second case re-examinatio t 21 years after the onset of chorea revealed systolic murmur and slightly bulgent left atrium but re-examination could eliminat the suspicion of R.H.D The third patient had chorea t 8 years with recurrence at 15 and 16 years and on re-examination t 33 years she was found t ha ystolic murmur grade II—III apically and loud first sound, but no diastolic murmurs.

Re-examination 5 years later showed signs of aortic incompetence but no evidence of mitral involvement. The first examination had show bulgent left trium which, however was not demonstrable t the second examination.

The cases regarded as uncertain R.H D because of uscultatory findings only consisted of 6 patients with systolic murmurs localised to the apex, where even examination by various

Table 11 Chorea minor
Results of the re-examination.

	Rheumatic heart disease.			Total
	Certain	Uncertain	Excluded	
♀	9 (19 6)	12 (26.1)	25 (54 3)	46
	4 (16.7)	5 (20.8)	15 (62 5)	24
Total	13 (18.6)	17 (24.3)	40 (57 1)	70

(Figures in brackets indicate percentages)

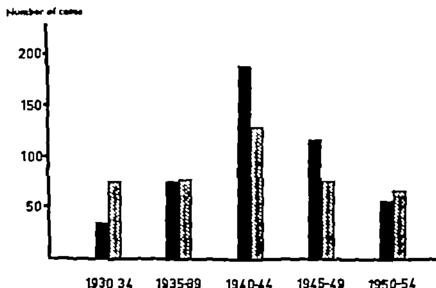


Fig. 18. The frequency of acut nephritis and erythema nodosum in females during 1930—54
Total number of cases with acut nephritis 469 (with scarlet fever 53) and with erythema nodosum 422 (with acute polyarthritis 23).

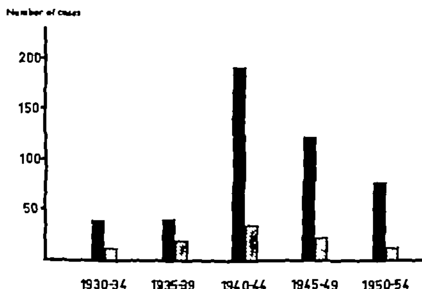


Fig. 19 The frequency of acut nephritis and erythema nodosum in males during 1930—54
Total number of cases with acut nephritis 467 (with scarlet f ver 156) and with erythema nodosum 97 (with acut polyarthritis 2).

Acut nephritis   Erythema nodosum

RESULTS AND COMMENTS

The present analysis of acut rheumatic fever is based on a series of patients admitted to Malmö General Hospital during the years 1930—54 The archives of the departments of paediatrics (including Rönneholms clinic) infectious diseases orthopaedics and medicine were searched. Th material includes all cases with a firm or doubtful diagnosis of acut rheumatic fever (including diagnoses and synonyms of acut polyarthritis acute endocarditis and chorea mino). Patients who were not residents of Malmö at the time of admission, were not included in the analysis and since the town of Malmö has only one hospital (no private hospitals) it may be assumed that the material studied is representative of the population.

Any clinical series covering such a long period must have some inherent sources of error Th clinical evaluation and criteria for the diagnosis of A.R.F has certainly changed though this is not directly apparent from the hospital records. The diagnostic methods available a generation ag were fewer and less refined than those nowadays used. The reason why all cases with a diagnosis of A.R.F were included was that it is so difficult to decide with certainty whether a diagnosis should be regarded as probable or firm.

It might be objected that it would have been better to limit the series to those cases in which the diagnosis could be considered as firm according to JONES modified criteria, but this was not possible because earlier investigations (BIDNCK et al. 1953) had shown that the group with a probable diagnosis of A.R.F had a higher frequency of R.H D than the population in general. In other words this group at least in some measure consisted of A.R.F and to xclude this group would be t exclude a group with A.R.F

Another source of error is a change in the frequency of hospitalisation during th period covered by the investigation. It is very difficult to judge this change which in some measure may be due to an alteration in the attitude of the population in general, to hospitalisation and to a revision in the principles of general practitioners when referring patients to hospital. Analysis of the records at the various departments however showed that the number of beds per 10 000 inhabitants had remained almost unchanged during the period covered by the investigation and an inquiry by questionnaire among practitioners showed that, broadly speaking, it was a rule to refer patients with suspected A.R.F to hospital. Formerly however when the only remedy available was salicylic acid doctors may have given their patients domiciliary treatment as is suggested by th fact that during the 30ies the frequency of probable and suspected cases was lower than during later 5-year periods.

The interpretation of the auscultatory phenomena has also varied considerably during th period of investigation. A systolic murmur irrespective of its localisation was regarded as pathologic to a much larger extent during the beginning of the period than during the end and auscultation played a much greater rôle in the diagnosis f the disease than it does today

below 20 and in patients who have the first attack above the age of 30 recurrences are rare.

About 40 per cent of the recurrences were noted within two years after the first attack, and 80 per cent within ten years.

The risk of developing rheumatic heart disease increased with every new attack (18 per cent after one 33 per cent after two and 41 per cent after three attacks).

The late mortality was low (6 1 per cent within 3—28 years).

The findings in the present investigations differed in the following respects from what is widely believed in this field.

All manifestations of acute rheumatic fever (acute polyarthritis acute endocarditis and chorea minor) increased during the years of the War

The decrease in the frequency of acute rheumatic fever was most marked after 1950 and during the last three 5-year periods of investigation it was 1.8, 1.3, 0 7 per 10 000 inhabitants per year

Age at onset of first attack in the group with polyarthritis is high (mean age about 25 years) but also in the group with acute endocarditis (mean age 17 years)

The frequency of recurrences (less than 25 per cent) was low during the investigation period and none of the patients admitted during the last 5-year period had a recurrence during that period (In patients admitted during 1930—54 the frequency of recurrences per 5-year period was 16.5—13.5—8.4—4 9—0 per cent in acute polyarthritis, and 8 7—7 0—2.4—1 6—0 per cent in acute endocarditis)

The frequency of rheumatic heart disease at the re-examination after 1953 for the entire group was 21 per cent. (In acute polyarthritis and chorea minor about 20 per cent and in acute endocarditis about 30 per cent) and the total frequency of R.H.D was 25 per cent in the group with acute polyarthritis, 37 per cent with acute endocarditis and 20 per cent with chorea minor (Fig. 16).

The frequency of acute rheumatic fever is decreasing and it might be assumed that rheumatic heart disease with time will also become rare.

cutaneous nodules were rare Despite geographical differences in the frequency of these manifestati ns it cannot be excluded that the lowness of the frequency might be due to the fact that such manifestations have not always been entered in the hos pital records.

Acute rheumatic fever is not difficult to diagnose if the patient has clear igns f active endocarditis but since 325 of 588 cases were diagnosed mainly on the presence of acute polyarthritis WALLGREN's (1057) question arises i e Should acute polyarthritis be regarded as a major mani festation or not? As long as A R.F is defined as a pre-stage of R H D attempts should be made to define A.R F as nar rowly as possible which is also stated by MITCHELL (1035) and FRIEDBERG (19 9). That this is necessary is apparent from the fact that in the group with acute poly arthritis the firm, probable and suspected cases were equally common during the last 5-year period From this study it is possible to conclude that if cute poly arthritis makes its first appearance after 30 years of age it rarely leads to R H.D (see p 95). Su h patients should therefore n t be regarded as having "pot ntial R.H D

INCIDENCE

The frequency of patients with a firm diagnosis tended to decrease from one 5-year period to another already during the 30ies while it sh wed a significant increase during the War and decreased substantially again afterwards. The inci d nce of acute rheumatic fever satisfying JONES' criteria will be as follows.

Firm diagnosis according to JONES criteria.

1930—34 2.5 per 10 000 inhabitants per year
1935—39 1 6 pe 10 000 inhabitants per year
1940—44 1.8 per 10 000 inhabitants per year
1945—49 1 3 per 10 000 inhabitants per year
1950—54 0 7 per 10 000 inhabitants per year

The decrease from 1930 was thus pronounced with a slight but significant ($P < 0.001$) rise between 1940—44 and a striking fall during the subsequent three 5-year periods. The obvious decrease in the incidence during the 30ies was due mainly to a decrease in the number of cases of acute endocarditis. The incidence of 0 7 per 10 000 inhabitants per year in the 1950—54 period was in good agreement with that reported by FLEMING et al. (1956) in Minnesota and since 1952 no new cases of chorea minor have been seen at the hospital.

It is not possible to hold any known particular factor responsible for the decrease during 1930—54 though a possible effect of antibiotics cannot be excluded.

The increase during the War was noted for acute polyarthritis acute endocarditis and chorea minor An increase in the fre quency of acute rheumatic fever during the War was also reported from Denmark by HARVING (1946).

SEX DISTRIBUTION

The sex distribution (females/males) in acute rheumatic fever satisfying JONES criteria was in patients with acute poly arthritis 1/0.9 and in those with acute endocarditis 1/1.3. No difference was thus found in the frequency between the sexes and even if the number of males with acute endocarditis was predominant for the 5—10 year age group the difference was not significant. For patients with chorea minor the distribution (females/males) of those with a firm diagnosis was 1 9/1

AGE DISTRIBUTION

The age distribution within the group with a firm diagnosis showed that patients with acute endocarditis had a mean age

tion with acute rheumatic fever while no such decrease could be found for R.H.D. HITCHENS (1956) showed that acute rheumatism with heart disease decreased during the 1931—50 period, and similar observations have been reported in Sweden by JACOBSSON (1946). EDSTRÖM & GEDDA (1954) found only a slight decrease in the cases of R.H.D. in an autopsy series from the years 1934—51 while WAALER (1958) could not demonstrate any such difference with certainty. WHITE (1953) was able to report a decrease in the frequency of R.H.D. in his private clientele on comparison between the years 1925 and 1950.

The incidence of R.H.D. has also been judged and calculated on the basis of other investigations and Sir JOHN PARKINSON (1945) reported that for the age groups 18 to 44 years the frequency of R.H.D. was 2.6 per cent. On the basis of these figures WOOD (1954) calculated that there should be 80 000 cases of mitral lesions requiring operation in England, which for Great Britain would give an incidence of 3.2 per 1 000 (BJÖRCK 1955).

The incidence of R.H.D. in Sweden has been calculated by BJÖRCK (1955) and the calculation is based partly on personal investigations and partly on WESTMAN's mass x-ray examination in Stockholm (1950) in which 1 out of every 1 000 was found to have roentgenological signs of mitral stenosis, and partly on the results of EDSTRÖM (1935). According to BJÖRCK's calculation, 2 persons out of every 1 000 should have asymptomatic mitral lesions and there should be an equal number with symptoms, i. e. a total of 4/1 000. In view of the different frequencies of A.R.F. in the country BJÖRCK gave 1.5/1 000 as the frequency of established mitral valvular disease in Sweden.

DISTRIBUTION OF VALVULAR LESIONS

The reason wh the right half of the heart i seldom in olved by acute rheumatic fever has been discussed and the difference in the vascularisation of the valves has been considered of importance (GROSS & KUGEL 1931) but it has not been possible for other research workers to confirm this assumption (WEARN et al. 1936). WOOD (1954) offered the following explanation. A 10-year old child has an arterial pressure of 100/60 mm Hg and a pulmonary pressure of 15/6 mm Hg, and the pressure against which the different valves have to work will be 70 mm Hg for the aorta, 100 mm Hg for the mitral, 15 mm Hg for the tricuspid, and 6 mm Hg for the pulmonary valve. According to this author this situation might explain the differences in the frequency of valvular lesions accounted for below.

AUTOPSY SERIES

In a series of 208 cases CABOT (1926) found the mitral valve to be involved in 85.6 per cent, the aorta in 44.7 per cent, the tricuspid in 15.9 per cent and the pulmonary in 1.9 per cent. EDSTRÖM & GEDDA (1954) reported in a series from 1934—51 (total of 367 cases) that the mitral valve was engaged in 87 per cent, the aortic in 51 per cent, the tricuspid in 7 per cent, and the pulmonary in 1 per cent.

CLINICAL SERIES

Clinical series of rheumatic heart disease must be of a different composition than autopsy series, for the latter include cases that have not been diagnosed clinically because the lesions had not produced clinical symptoms or signs, because of misdiagnosis or because the patients had not been examined etc. In EDSTRÖM & GEDDA's series 27 per cent had not been diagnosed clinically. HIRSCHFELDER (1918) whose series consisted of 1 781 cases of R.H.D. reported that 51 per cent had an affection of the mitral valve only, 20 per cent of the aortic valve only, and 20 per cent of the mitral and aortic valve, while WHITE & JONES (1928) gave the following figures: 56.3 per cent with involvement of the mitral valve only, 14.7 per cent with

primary mortality and a total mortality of 23 per cent after 6—23 years of observation but the material covered the years 1926—40. McCut et al. (1948) described a total mortality of 7.1 per cent and Saslaw et al. (1950) reported a similar mortality.

Of the 30 patients who died after the first admission for A.R.F. and not during an attack of this disease it has been possible to reveal the cause of death in 35. 14 patients have been autopsied and all have had signs of R.H.D. and 4 died in hospital (without autopsy) and the cause of death was R.H.D. in 3. Of 17 patients who died outside the hospital 7 have had the diagnosis of R.H.D. in the death certificates. Thus a total of 24 (4.1 per cent) patients in group A have had R.H.D.

RESULTS OF THE RE-EXAMINATION

RHEUMATIC HEART DISEASE, CERTAIN

At the re-examination in 1953 or later it was noted that 19.7 per cent of the patients who had had acute polyarthritis had signs of R.H.D., while the corresponding figure for acute endocarditis was 20.8 per cent, for chorea minor 18.6 per cent. For the total group with firm diagnosis of A.R.F. according to Jones modified criteria we can calculate that the total frequency of R.H.D. is about 25 per cent (21 per cent at the re-examination and 4 per cent dead) and that this figure is minimal because no data were available for the patients who could not be traced because of incomplete data. The frequency of certain R.H.D. was not higher for the group with both acute polyarthritis and acute endocarditis than for the group with endocarditis only (29 per cent at the re-examination and 8 per cent dead).

Edström (1935) and Jacobsson (1946) found a much higher frequency of R.H.D. — 53.0 per cent and 62.0 per cent, respectively — but the difference is due to much higher frequency of the diagnosis of mitral incompetence in those two series compared with that in the present material and if the figures be corrected accordingly there will be about 25 per cent and 27.0 per cent respectively which agrees well with those found in the present material. Bland & Jones (1952) also described a higher frequency of R.H.D. after an observation period of 20 years but there too mitral incompetence was common. The difference between their material and the present material may be due to the difference in the selection of cases since they collected only patients with acute endocarditis at the age below 20. Bland & Jones (1952) found that clear-cut auscultatory signs of mitral stenosis and aortic diastolic murmurs of grade II showed no tendency to regress while the systolic apical murmur which was interpreted as mitral incompetence could disappear or develop into mitral stenosis. In the present material there were no cases which showed regression when the roentgen examination showed an enlargement of the left ventricle and/or left atrium and the electrocardiogram showed left hypertrophy. It would be desirable in the interest of the patients and to enable comparisons of different reviews, to limit the diagnosis of chronic M.I. to cases with a pan-systolic apical murmur audible out in the left axilla (Leatham 1958) and with roentgenologic or electrocardiographic signs of left heart strain, though it implies a risk of under-diagnosis. The risk is, however not so very great, since mitral incompetence was rarely demonstrable in the clinical and the autopsy series.

RHEUMATIC HEART DISEASE, UNCERTAIN

In addition to the group with a firm diagnosis of R.H.D. there was a group with uncertain R.H.D. which consisted of patients with auscultatory and/or roentgen abnormalities. In the group with acute polyarthritis the frequency was 15 per cent, in the group with acute endocarditis 21 per cent and in the group with chorea minor 24 per cent. About half of these cases have been included here, because of suspected roentgen findings which on later re-examination proved not to be of patho-

found between different types of aortic stenosis at autopsy It is not easy to decide the aetiology in patients with markedly calcified and deteriorated valves. In a clinical series of 250 cases of aortic stenosis 54 were congenital but the majority of the latter were subvalvular and the remainder were regarded as rheumatic (Wood 1958) Bedford & Caird (1960) write after a careful analysis of the literature that even if the cause is rheumatic, aortic stenosis as an isolated valvular lesion represents a distinct entity requiring separate treatment Aortic stenosis combined with other valvular lesions is clinically more comparable with pure mitral stenosis than with pure aortic stenosis (Mitchell et al. 1954)

The commonest causes of aortic incompetence are rheumatic fever or syphilitic aortitis, other causes are rare — arteriosclerosis coarctation of the aorta, malformation of the aortic valves hypertension Marfan s syndrome dissecting aortic aneurysm etc. (Bedford & Caird 1960). The aortic incompetence with or without stenosis is caused by rheumatic fever in 67 per cent by syphilis in 10 per cent and by arteriosclerosis in 7 per cent (Campbell et al. 1932) and in 100 cases in the series of Segal et al. (1956) 83 were rheumatic 12 syphilitic, 4 congenital and 1 traumatic.

MITRAL VALVULAR LESIONS

Pure mitral incompetence is rare as previously mentioned, but Wood (1956) found mitral incompetence to be the "major hemodynamic fault in 34 per cent of a series of 300 patients with mitral lesions. The clinical diagnosis of mitral incompetence has however varied considerably in the course of years and opinions still differ particularly regarding the evaluation of the auscultatory findings (Bedford & Caird 1960). It is therefore not remarkable that the literature gives such figures as 177 cases of mitral incompetence of 271 cases with mitral lesions (Edstrom 1935) while Biörck et al. (1955) gave only 5 of 134 This remarkable situation cannot be ascribed to geographical differences, because both investigations were carried out in the south of Sweden the difference must therefore be attributed to differences in interpretation of the auscultatory findings. White (1951) stressed that mitral stenosis occurs with or without incompetence and that only in rare instances does pure mitral incompetence occur

Mitral incompetence is less common among females than among males the sex ratio being 2/3 (Wood 1954 Bedford & Caird 1960) while mitral stenosis shows the opposite ratio namely 2.5/1 (Olesen 1955) 4/1 (Nylin 1952) 4 4/1 (Biörck et al. 1955). Brigden & Leatham (1953) found the sex distribution in pure mitral incompetence to be 1 female to 5 males and Wood (1954) gave a corresponding ratio of 4/1 for pure mitral stenosis and 3/1 for stenosis with mild incompetence and 1/1 for stenosis with severe incompetence

PROGNOSIS

The prognosis of mitral incompetence according to Wood (1956) is the same as for mitral stenosis in that the initial inflammation occurs at the same time in both types of valvular disease and that the mean age at death is roughly the same There is a difference between mitral stenosis and mitral incompetence in that the asymptomatic period is longer in mitral incompetence but the downhill course is more rapid (Brigden & Leatham 1953 Wood 1956) Brigden & Leatham also state that the natural history of mitral incompetence is often interrupted by bacterial endocarditis.

The prognosis of mitral stenosis has been judged by Olesen (1955) and he claims that no systematic clinical in

logic significance (HALL et al. 1961). In other words the number of uncertain cases of R.H.D. would be about 10 per cent which is the same figure as JACOBSSON (1946) arrived at for the group of possible heart disease.

The mean interval between the first attack and the re-examination was for the group with certain R.H.D. 16.3 years, for the group with uncertain R.H.D. 11 and for the excluded group 13.6 years. Since no significant difference was found between the frequency of R.H.D. with n 12.4 years and 23.7 years respectively after the first attack in the group with chorea minor there is hardly any reason to expect any appreciable increase in the frequency of R.H.D. with increasing observation time in the excluded group. This was also borne out by the fact that no difference was found in the frequency of R.H.D. in the two groups of acute polyarthritis admitted in 1945—49 and examined in 1953 and 1959 respectively. Later check examination showed that uncertain R.H.D. relatively seldom progressed to certain R.H.D.

VARIATION OF FREQUENCY OF RHEUMATIC HEART DISEASES WITH RECURRENCES OF ACUTE RHEUMATIC FEVER

There was no significant difference between the mean ages at the time of the first attack of A.R.F. between the groups with certain, uncertain and excluded R.H.D. The mean age was 19.1 for certain R.H.D., 15.6 for the uncertain and 21.6 for the excluded group. The mean age was somewhat higher for the last mentioned group but the difference was not significant. The question arises whether as found by BLAND (1955) patients with valvular disease had more recurrences than those without.

Variation of frequency of rheumatic heart diseases with recurrences of acute polyarthritis

Number of attacks	Number of cases	R.H.D.
One	172	25 (14.5)
Two	49	16 (32.)
Three or more	29	12 (41.4)

(Figures in brackets indicate percentages)

The table above gives the frequency of R.H.D. in the group with a firm diagnosis of acute polyarthritis with or without acute endocarditis after one, two and three or more attacks.

The difference in frequency of R.H.D. after one and two attacks respectively is significant ($P<0.01$) but not the difference between the frequency after two and three or more attacks.

The corresponding frequencies for the group with acute endocarditis with or without acute polyarthritis at the time of the first attack were 26.8, 3?.0 and 50.0 per cent. The frequency thus tended to increase but not significantly with the number of recurrences. This group is however not large enough to allow of any valid conclusion. FEINSTEIN et al. (1959) concluded that in the absence of signs of heart disease at the end of an attack heart disease will not develop. However neither the present investigation nor that by JACOBSSON (1946) provided any support for the above-mentioned conclusion. It is not possible to say whether this discrepancy might be due to differences in composition of the materials.

PROBABLE RHEUMATIC FEVER

The group with probable rheumatic fever — group B — consisted of a total of 4?0 cases. Of these a diagnosis of acute endocarditis and acute polyarthritis had been made in 43 (9.2 per cent), acute endocarditis in 28 (6.0 per cent), acute

arrived at the conclusion that the surgical results were good even if the operative mortality was included.

Further data on the operative series of mitral stenosis are given in the chapter on the operative series.

AORTIC VALVULAR LESIONS

Pure chronic rheumatic aortic incompetence is less common than aortic stenosis, and in Wood's material it occurred in the ratio 1/2 (Wood 1958). Clinically demonstrable aortic incompetence occurs in combination with aortic stenosis in varying frequency, thus for example McGinn et al. (1934) gave 22 per cent, Bergeron et al. (1954) 65 per cent, and Bedford & Caird (1960) in a series of 132 cases above 65 years of age 63 per cent. In his series Mitchell et al. (1954) found 131 cases of pure aortic stenosis and 224 of aortic stenosis with incompetence.

Aortic incompetence is less common among females than among males and in Wood's material the sex ratio was 1/2 (Wood 1958) and the sex distribution was the same as for aortic stenosis, namely 1/2 (Wood 1958). Other series gave a somewhat higher frequency for males, namely Lewes (19 1) 1/3, Schjødt (1956) 1/3, Olesen & Warburg (1958) 1/3, while Karsner & Koletsky (1947) gave 1/1.6 after correction for the sex distribution of the population and Aastrup et al. (1952) gave about 1/2 and Müller (1956) gave 86 females and 91 males.

PROGNOSIS

The prognosis of pure rheumatic chronic aortic incompetence is according to Wood (1958) about 20 to 30 years from its development and the prognosis can be judged by the size of the left ventricle and by the degree of incompetence as estimated from peripheral vascular changes. White (1951) states that slight aortic incompetence is compatible with a long and active life and need not produce any symptoms, while the grave form of aortic incompetence represents a greater burden than the aortic stenosis. Grant (1933) who studied 71 males with rheumatic aortic incompetence with a mean age of 29.4 years at the time of the first observation, found that after 10 years 33 per cent died while 34 per cent showed no progression of the disease. The risk of bacterial endocarditis is also apparent from that investigation, in which 12 per cent had this complication during the period of observation. In a series of Segal et al. (1956) which included 83 cases of rheumatic and 17 of aortic incompetence of other origin, the symptomatic period varied from 2 months to 30 years (average 6.4 years). This group however contained only severe cases with a mean age of 34 years.

It is now generally accepted that the aortic stenosis develops gradually during a period of many years and that it is then asymptomatic for several years and produces symptoms for a few years before it finally results in death. Bland, White & Jones (1935) claimed that it took at least 2 years for mitral stenosis to develop. There are a number of observations on record in which patients with systolic murmur in youth later developed aortic stenosis (Baker et al. 1943, Levine & Harvey 1949, Wood 1958) and Wood (1958) concluded that trivial aortic stenosis can take anything up to 40 years before it produces any haemodynamic symptoms. There are, however, signs which suggest that aortic stenosis can develop much more rapidly, and Grant (1933) found that patients with aortic incompetence can develop aortic stenosis within 10 years. Bedford & Caird (1960) stressed that even elderly patients can develop aortic stenosis within 2—5 years and that it is difficult to believe that a rheumatic process can be so active in elderly persons.

The prognosis of aortic stenosis is based

patients with acute polyarthritis associated with erythema nodosum is thus small. Therefore erythema nodosum should hardly be forthwith regarded as evidence of A.R.F. which has been pointed out previously by Dæhn (1941).

A search of the records at the various departments studied (page 12) revealed a total of 422 females and 97 males with erythema nodosum. Figs. 18 and 19. Rheumatic fever had been suspected in 45 of the 422 females and in 6 of the 97 males. Löfgren (1946) found 2 per cent of the patients with erythema nodosum to have signs of joint swelling and in a later study (1953) he reported that out of 21 patients with bilateral hilar gland enlargement 113 had erythema nodosum and 8 joint swelling. Erythema nodosum and joint swelling have been mistaken for rheumatic fever (Löfgren 1953) and since this group increased with the frequency of streptococcal infection during the War it seems likely that these skin and/or joint manifestations were of streptococcal origin. It can, at any rate, not be ascribed to tuberculosis, since there was no appreciable increase in that disease during the War in the hospital.

Figs. 18 and 19 also show the frequency of the diagnosis of acute nephritis (including scarlet fever nephritis) for the same period. It is clear that their frequency also showed an increase during the War. It thus appears that the years of the War witnessed an increase not only in the frequency of manifestations of acute rheumatic fever but also of other conditions ascribed to streptococci.

There may be other diseases in this group such as sarcoidosis (Truelove 1960) and postinfectious rheumatism (Jonsson 1960).

The fact that the probable group did not consist entirely of diseases other than rheumatic fever is apparent from the frequency of valvular lesions at the re-examination.

RESULTS OF RE-EXAMINATION

At the re-examination in 1953 or later it was noted that 7 per cent of those with acute polyarthritis had signs of R.H.D., 14 per cent of those with acute endocarditis and 0 per cent of those with chorea minor.

The frequency of R.H.D. for the entire group with a probable diagnosis of rheumatic fever was 10 per cent which compared with the corresponding frequency in the group with a firm diagnosis would mean that one third of the cases in this group had rheumatic fever if the frequency of organic lesions is independent of the severity of the disease. Here too the earlier the onset of rheumatic fever the greater the risk of R.H.D. and all of the cases with R.H.D. at the re-examination had the first attack before the age of 20.

SUSPECTED RHEUMATIC FEVER

In the third group of rheumatic fever, the so-called suspected group — group C — there was a total of 306 cases. In 17 of them the diagnosis of acute endocarditis and acute polyarthritis had been made, acute polyarthritis only in 222 and acute endocarditis only in 6. The frequency of the diagnoses was not found to vary with sex. The suspected group showed a relative increase from one 5-year period to the next, and during the last 5-year period, there was 1 probable and 1 suspected case for every firm case of A.R.F. The age distribution of group C showed no marked peak but was fairly even from the 5—9 to the 50—59 year age class. At the re-examination only 1 patient in the group with acute polyarthritis was found to have R.H.D. and 23.4 per cent showed evidence of rheumatoid arthritis. In the

58 and 62 years respectively and for combined aortic and mitral stenosis 60.5 and 62.5 respectively *i.e.* the combination has a somewhat higher mean value than pure mitral stenosis only.

The literature studies showed a good correlation regarding many details of the course of R.H.D. but the writer has not been able to find any series which could with certainty be regarded as emanating from the same population and covering both acute rheumatic fever and rheumatic heart disease.

majority of th cases the diagnosis of rheumatic fever had been based on ar thralgia in association with pneumonia pulmonary tuberculosis malignant disease blood diseases etc. In the group with a diagnosis of acut endocarditis th ituation was somewhat different and as is apparent from Fig. 10 as many as 30 per cent were found to have a valvular lesion either at th re-examination or at autopsy This may be explained by the fact that in the presence of valvular disease with associated bscure condi tions e g. idiopathic fever the possibility of rheumatic fever is usually consid red. This is intimately connected with th problem of re-stenosis after commissurotomy and will be discussed further n the chapter on the operated series.

As is clear from the autopsy findings in this group of suspected rheumatic fever cases of bacterial endocarditis are suspec ted to have rheumatic fever

Finally 2 of the cases that proved to have R.H D at the re-examination had their first attack before 1930 but never showed a characteristic clinical picture of the disease while the remainders who had a high E.S.R. in association with acute tonsillitis were suspected of having acute ndocarditis. These patients illustrate the difficulty in making a diagnosis of rheumatic fever and might also help to explain why about 50 per cent of the patients with R.H.D report that they had not had rheumatic fever

SUMMARY

Malmö is ne of th few towns in th world that is really suitable for epidemiological investigations because the town has only on hospital and that hospital caters for a population of more than 200,000 inhabitants This advantage was therefore utilized to study the natural history and the prognosis of acute rheu matic fever

The hospital records and parish registers were studied for th subsequent course of cases of acute rheumatic fever admitted to Malmo General Hospital in 1930—54 and representative groups of the survivors were reviewed in 1953 and later

Th material was divided int three groups according to the firmness f the diagnosis (firm probable suspected). The firm group satisfied Jones modified criteria.

The suspected group consisted mainly f patients with diseases ther than acute rheumatic fever while the probable group comprised at least a certain percentage of cases of A.R.F since the frequency of R H D t the review was higher than that for the population as a whole During the last 5-year period the frequency of firm probable and suspected diagnosis was equal.

Below the observations in the firm group made in the investigation are briefly outlined against the background of publications by earlier workers in this field.

Good agreement with the r ports of previous invest gators was found in the following respects.

The frequency of th disease was decreasing.

Th acute mortality is low and decreasing, less than 2 per cent — somewhat higher among females than among males (in acute polyarthritis 1 2 per cent, in acute endocarditis 7 per cent and in chorea minor 4 per cent)

Sex distribution — equal, except in chorea minor in which it was 1.0 1 (females/males)

Mean age at onset of chorea minor 9 ~ years

The elevation of E.S R. and AST

Patients with the first attack of A.R.F after th age of 30 rarely develop rheumatic heart disease

Of all recurrences, 80 per cent were seen in patients who have had the first attack

	M.S.	M.S. M.I.	M.I.	Total number[1] of patients
Females	376 (30)	350 (20)	129 (20)	855 (79)
Males	140 (22)	133 (4)	79 (12)	352 (38)
Total	516 (52)	483 (24)	208 (41)	1207 (117)

(Figures in brackets indicate patients in whom diagnosis was with a question-mark)

[1] Insufficient data were available about 6 females and 6 males.

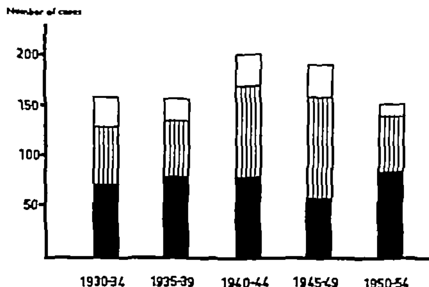


Fig. 20. *Rheumatic heart disease.*

Distribution of mitral lesions in females on first admission during 1930—54.

Total number of cases 855.

Stenosis | Stenosis and incompetence | Incompetence

ses of M.S. and M.S. M.I. per 5-year period from 1930 had been made in 129 females during 1930—34 134 during 1935—39 168 during 1940—44 156 during 1945—49 and 139 females during 1950—54 respectively. The diagnosis of M.S. was predominant during the 30ies and 50ies, that of M.S. M.I. during the 40ies. The corresponding figures for the males were 52, 53 65 58, and 45 and here too the number with a diagnosis of M.S. M.I. was highest during the 40ies. For both females and males the frequency diminished during the last three 5-year periods. A diagnosis of M.I. was made with fairly equal frequency until the 50ies in the female group after which it fell, and was made in 30 during 1930—34 22 during 1935—39 32 during 1940—44 32 during 1945—49 and 13 during 1950—54. The same tendency was noted for males 26 12, 19 16 and 6.

The age distribution of the females and males at the time of first admission is given in Figs. 22 and 23. In both sexes the frequency showed a peak for the 40—49 year group. It was, however not so

PART II

RHEUMATIC HEART DISEASE

SURVEY OF THE LITERATURE

INTRODUCTION

The term rheumatic heart disease (R.H.D.) is t be understood her as referring only to hronic valvular organic changes and not to the acut or subacute forms (see Chapter n Definitions) Desp t this limitation which proved necessary it is hardly possibl to give anything lik a complete survey f the literature WHITE (1951) stated that alvular disease of the heart is an important subject for consideration not only because it is often the primary cause of heart failure but also there is much unnecessary confusion associated with it in the medical literature and in the minds of physicians Limitation f the term to chronic organic valvular changes f so-called rheumatic type might h lp to decrease the confusion and since valvular changes are accessabl to surgery it wa decided to adopt this limitation. Since the valvular structure of the right side of th heart is seldom involved by acute rheumatic fever (A R F) interest will be given mainly to aortic and mitral lesions.

INCIDENCE AND FREQUENCY

It is difficult to judge th frequency of chronic h umatic valvular heart diseases because as pointed ut by CLAWSON (1941) no true data are available on the incidence of the disease and no investigations have apparently been performed on rand m aut psy series. CLAWSON also stated that the relative frequency of different types of heart diseases varies not only from one country to another but also in different parts of one and the sam country CLAWSON (1941) reported on a series of 30,265 autopsies (females/males — 1/2) and found a frequency of 870 cases of R.H D i 2.9 per cent from Minnesota, whil CLELAND in Australia (1934) reported 2.9 per cent and EDSTROM & GEDDA (1951) and HALL et al. (1952) 3 7 per cent and 4.5 per cent respectively for the south of Sweden GELFMAN (1943) gave a frequency of 5.5 per cent for an autopsy series in Boston, CLAIBORNE et al. (1941) 3.5 per cent in Atlanta while DECHERD et al. (1943) and BRUNO et al. (1942) gave 0 0 per cent and 0.6 per cent for Galvestone and New Orleans respectively

In some geographic regions R.H.D is rare as in Switzerland for example and in the places referred to above while such countries as the British Isles Italy and New England have a high frequency and Sweden occupies an intermediate position (BIORCK 1935).

The incidence of R.H D has not remained constant in the course of years but the figures are based on both acute and chronic forms of R.H.D HEDLEY (1939) was the first to note a decrease in the frequency and in American vital statistics there are still signs of a further decrease (U.S National Office of Vital Statistics 1956) KNOWELDEN (1949) found a decrease in the frequency of R.H.D in England during the years 19?0—38 in associa

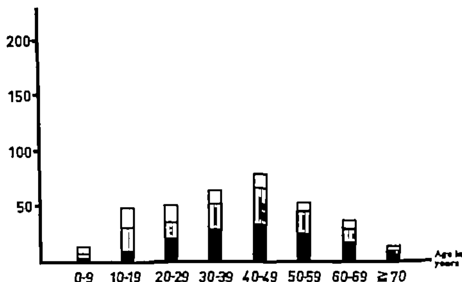


Fig. 23. *Rheumatic heart disease.*

Age distribution f mitral lesions in males on first admission during 1930—54.

Total mber of cases 332.

Stenosis | Stenosis and incompetence | Incompetence

marked for the males. It is noteworthy that the number of cases in the 10—19 year group was larger for males than for females while in all the other groups females were predominant There were only 6 (1 6 per cent) females below 20 with a diagnosis of M.S the figures for the subsequent 10-year groups being. 10 4 per cent between 20—29· 20 7 per cent between 30—39· 23.0 per cent between 40—49· 21 0 per cent between 50—59· 14 6 per cent between 60—69· 7 7 per cent for the ages above 69 years. Of the 140 males with M.S., 12 (8.6 per cent) were below 20 years the frequencies for the subsequent 10-year groups being fairly equal, namely 14.3—20 7—23.6—17 1 per cent until the age of 60 when the frequency dropped to 11 4 per cent and in patients above 69 it was 4.3 per cent The age distribution of patients with diagnosis of M S M.I. was largely the same as for the patients with mitral stenosis nly and roughly the same for the 350 f males and the 133 males.

A total of 202 patients 115 females and 87 males had mitral *and* aortic lesions. All of the patients had on at least one occasion, had both diagnoses. The distribution per 5-year period for females was: 21 during 1930—34 24 during 1935—39 31 during 1940—44 18 during 1945—49 and 21 during 1950—54 The correspond ing figures for males were: 17 25 19 17 and 9 The age distribution showed that only a few patients were below 20 years at the time of first admission namely 4 females and 6 males and that the cases were equally distributed per 10-year period without any appreciable maximum for females or males.

PURE AORTIC LESIONS

During the 1930—54 period 162 patients had been treated who on the first admission had had a diagnosis of pure aortic lesions. A diagnosis of A.S. had been made in 51 of A.S A I. in 49 and of A.I in 52.

affection of the aortic valve only and 28.0 per cent with involvement of mitral and aortic valves in a series of 1 09 cases. Directly corresponding figures from an autopsy series e g EDYNTHOM & GEDDA (19 1), gave the f llowing values mitral valve only in 41 per cent aortic nly in 9 per cent and mitral and aortic in 38 per cent

AETIOLOGY

About 50 per cent of patients with mitral lesions hav acute rheumatic fev r in the history (OLE EN 19 5 WOOD 19 6 BEDFORD & CAIRD 1960 ANSCHUTZ 1960) while the frequency is much lower f r those with aortic lesions namely 30 30 per cent (WOOD 1956 OLESEN & W R BERG 1958). The frequency f A R F n the history is low in patient with pure organic chronic mitral incompetenc (BRIGDEN & LEATHAM 1953) while 60 per cent of patients with mitral stenosis with or without incompetence ha e A R F in their history (OLESEN 1955) Pure organic aortic incompet nce is according t CAMPBELL et al. (1932), ascribable t rheumatic fever in 87 per cent while only 20—30 per cent f patients with aortic stenosis have a history f A.R.F (WOOD 1956, OLESEN & WAR ER 1958). The occurrence of acut rheumatic fever in the hist ry of patients with R.H.D decreases with increasing age and BEDFORD & C IRD (1960) were able to show that in patients between 65 and 80 years 46 per cent had had acute rheumatic fever as against 22 per cent in age classes above 80 The number of valves attacked also influences the frequency and ANSCHUTZ (1960) reported 100 per cent for aortic-mitral tricuspid lesions 85 per cent f r aortic mitral lesions and 63 per cent for mitral lesions.

The frequency of a history of A.R.F in patients with R.H D has not changed during the years 1934—61 as is apparent from the investigation of EDYNTHOM & GEDDA in 1934

If mitral tenosis may be regarded as the result f rheumatic fever in 50—60 per cent th aetiology of the other cases cannot be estimated with certainty (OLESEN 1955) The congenital form, which usually occurs in association with other malformations is believed to be rare (EMERY & ILLI OWORTH 1031) and even the sclerotic type does not play any important rôle (GRILL 1051).

The frequency of A.R.F in the history of patients w th pure organic mitral incompetence is low and its sex distribu tion i different from that of the remaining patient with mitral lesions namely 1 females males which induced BRIGDEN & LEATHAM (1953) to suppose an aetiology resembling that of aortic stenosis. Pure organic mitral incompetence is rare and mitral lesions usually consist of stenosis with or without a varying degree of incompetence (WHITE 19 1). BEDFORD & C IRD (1960) were unable to show a low frequency of A.R.F in the history f patient with mitral incompetence They arrived at a figure of 72 per cent, but the sex distribution in their series was 2 3 females males.

The aetiology of aortic stenosis has been nd is a question of debat and in principle 3 aetiological factors hav been discussed, namely rheumatic fever congenital deformation, and arteriosclerosis or atheromathosis. CLAWSON et al. (1938) concluded that the majority of patients with aortic stenosis had a rheumatic disease a conclusion also arrived at by KARSNER & KOLETSKY (1947). MONCKEBERG (1901) found the above-mentioned inflammatory as well as the sclerotic form. The last mentioned aetiological possibility has been advocated by several authors (GIBBS 1935 LENNICK & SCHLESINGER 1938 HULTGREN 1948 and others). As stated by BEDFORD & CAIRD (1960) many of the older investigations did not take into account the congenital form and in addition limited themselves to cal cereous disease of the aortic valve WOOD (1956) says that even if differences can be

Apart from the difference in number between the sexes the age distribution and the distribution per 5-year period were almost the same for females and males so that these groups could be taken together in these respects (Figs. 24 and 25) There was a slight increase from 20 21 26 during the first three 5-year periods to 48 and 39 during the last two. The frequency with which A.I. was diagnosed increased particularly during the 1950—54 period which may be explained, at least in part, by the fact that the heart laboratory was opened up in 1951

The age distribution at the time of the first admission is given in Figs. 26 and 27 The diagnosis of A.S. in females and males was rare below the age of 40 — only 4 of 51 cases, 5 in the 40—49 year group after which it increased to 12 in the 50—59 year group and to 18 in the 60—69 year group and 12 in the group of patients 70 years of age or more. Aortic stenosis was thus most common in patients above 50 years (82.4 per cent) on first admission and the highest frequency was noted for the 60—69 year group

5 patients below 20 years had a diagnosis of A.S. A.I., 8 between the age of 20—39 after which the frequency increased, 7 in the 40—49 year age group 13 in the 50—59 year age group 9 in the 60—69 year age group and 7 in patients above 69 Finally the diagnosis of A.I. in patients above 20 was equally distributed with values of 10 between the ages of 20—29 6 between 30—39 8 between 40—49 8 between 50—59 9 between 60—69 and 8 above 69 years and only 3 before the age of 20.

NON-SPECIFIED VALVULAR LESIONS

In addition to the afore-mentioned cases with a diagnosis of mitral or aortic valvular lesions there was a group with non-specified valvular lesions which very probably included cases of rheumatic valvular disease. Congenital heart disease — certain or suspected — and syphilitic lesions, was excluded from the analysis. In 1953 a total of 82 cases with a clinical diagnosis of certain or uncertain congenital lesions were examined and only in 1 case was it possible to establish a diagnosis of rheumatic valvular disease so that this group can hardly be a source of error in the calculation of the frequencies.

The group of non specified valvular disease included 217 females and 152 males. Of 217 females with a diagnosis of valvular disease, 58 (26 7 per cent) had the diagnosis with a question-mark and the corresponding figure for the males was 58 (38.2 per cent).

In both sexes the frequency was highest in the 1945—49 year group after which it decreased. The figures for the 5-year periods in females were 36 during 1930—34 42 during 1935—39 49 during 1940—44 61 during 1945—49 and 29 during 1950—54 and the corresponding figures for males were 29 24 22, 50 and 27 There was thus a substantial decrease in the group of non specified cases during the last 5-year period, which is, at least to some extent due to the inauguration of the heart laboratory in 1951 Many of these patients were below 20 years. There were thus 32.3 per cent (70 females) and 38.2 per cent (58 males) below 20 at the time of first admission and the largest group was that between 5 and 9 years. Otherwise the distribution of this group was even with 11.5 per cent females and 5 9 per cent males in the 20—29 year group 11 1 and 11.2 per cent, respectively in the 30—39 year group 13 4 and 14.5 per cent, respectively in the 40—49 year group 12.9 and 9 7 per cent, respectively in the 50—59 year group 12.0 and 14.5 per cent, respectively in the 60—69 year group and 6.9 and 3.9 per cent, respectively in the group above 69 years.

The age distribution is such as to suggest that a fair portion of the patients in the lower age groups also had acute rheumatic fever or acute endocarditis while only 5 females and 10 males out of 70 females and 58 males had a diagnosis suggesting rheumatic fever

vestigations have earlier been published on th prognosis of R.H D The figures given for the prognosis of mitral stenosis are presented below Readers interested in further details are referred to OLESEN s paper 1 which reference will often be made in subsequ nt sections (OLESEN 1955)

Age and time of death n cl ical serie and autopsy series

Clinical series	*Mean age at death*	*Number of patients*	*Per cent above 50 years*
DeGr and Levoo (1935)	33	402	1
CRA (1933)	40 9	100	
WILLIUS (1927)	41 6	164	19
LASTRUP (1937)	42.7	84	3
WOOD (1951)	39 3	300	
WILSO et l (1934)	43 8	121	34
OLESE (1955)	47 0	189	42
HALL et al (1958)	50.8	62	
Autopsy series			
CABO (1914)		21	28
KIRK (1919)		180	44
ZAFFKE t l (1939)	59 1	131	—

The most important milest nes in the natural history of mitral stenosis are age at the first attack f acute rheumatic fever (possibly recurrences) at the first symptom, at the first attack of right h art failure and at death. The age and the time of the initial attack of rheumatic fever was 12 years in WOOD s (1954) series and 15 4 in OLESEN s (1955) series while the first sympt m appeared at the age of 31 in th former series and at 31 2 years in th latter WOOD (1954) then stated that 7.3 years lapse from the onset f the initial symptom until total incapacity while OLESEN (1955) ga a mean age of 45 6 for right heart failur and of 4 0 for death. HALL & BIORCK (1958) described a series of 42 cases of mitral stenosis in patients f various ages and gave the following values rheumatic fever 17 9 years symptoms 40 7 years, failure 46 7 years and death 50 6 years and they could also show that the prognosis had probably improved during the period 1930 51

age at total incapacity

Prognostically important signs according to OLESEN (1955) are as follows.

Group		*Median survival time*
A	Patient in functional class II with sinus rhythm	20 years
B	Patient in functional class III with sinus rhythm	5—8
C	Patient in functional class II with auricular fibrillation	5—8
D	Patients in functional class IV	1

Further details will be given in subsequent sections.

PROGNOSIS AFTER OPERATION

Figures and data on th natural history of mitral stenosis treated conservatively after 1950 are not complete and not r liable because so many cases of mitral stenosis have been subjected to operation during last decade BAKER (1960) surveyed th literature and found that between 70—80 per cent of patients operated upon became better and that the operative mortality which was low already in the beginning, namely 15 per cent had fallen to about 5 per cent (2 per cent in BAKER series). Attempts have been made t compare mitral stenosis treated conservatively and surgically by DONZELOT et al. (1958) who for example found that of 165 patients perated upon 16 died while of 19 who refused operation 11 died. ELLIS, HARKEN & BLACK (1959) reported 1 000 operated cases during the years 1949—56 and believed that the survival was better than what could have been expected from conservative treatment. The operative mortality was 0.8 per cent in the last 500 cases. These authors also stated that it was difficult to obtain data on the survival rate of conservatively treated mitral stenosis and made a comparison with OLESEN's (1955) series and

FREQUENCY OF THE DIAGNOSIS OF RHEUMATIC HEART DISEASE CLASSIFIED ACCORDING TO DEGREE OF FIRMNESS OF DIAGNOSIS

The number of cases of R.H.D per 5-year period from 1930—54 was largely the same until 1950 after which it diminished considerably Since it might be claimed that this reduction in the number of cases diagnosed may be due to modifications and improvements in diagnostic methods the patients were divided into 3 groups according to the firmness of the diagnosis. (See Chapter on Definitions)

The clinical data available on 45 patients or 2 6 per cent of the entire material of 1 740 patients were incomplete The total number in the respective groups were: Group A 1 985 (58 1 per cent) group B-1 432 (25.5 per cent) and group C 1 278 (16.4 per cent). It is clear from Figs. 28 and 29 and the data given below that the number of patients in group A 1 — firm diagnosis — showed an even increase until 1950 and then a decrease while group B-1 — probable diagnosis — as well as group C-1 — suspected diagnosis — showed an increase in frequency until the 40ies compared with previous years and then a decrease The number of cases in group A 1 (females and males) was 174 during 1930—34 187 during 1935—39 194 during 1940—44 232 during 1945—49 and 198 during 1950—54 The corresponding numbers in group B-1 were 95 71 102, 97 and 67 and in group C-1 45 45 79 70 and 30

The afore mentioned figures for the 5-year periods give the following figures for the incidence per 10 000 inhabitants per year for rheumatic heart disease in group A 1 B-1 and C-1

1930—34	4 9	(322/131 000[1])
1935—39	4 2	(312/148,000)
1940—44	4 7	(383/163,000)
1945—49	4 7	(423/182 000[1])
1950—54	3.0	(300/201 000)

and the corresponding figures for all cases with a firm diagnosis — group A 1 — were·

1930—34	2.7	(174/131 000[1])
1935—39	2.5	(18 /148 000[1])
1940—44	2.4	(194/163 000[1])
1945—49	2 6	(232/182,000)
1950—54	2.0	(198/201 000)

The largest decrease in frequency of the number of patients with valvular lesions was due to a decrease in the number of probable and suspected cases but even those with a firm diagnosis showed a decrease which was significant ($P < 0\ 01$) during the last 5-year period. The group with a firm diagnosis consisted of 55.4 per cent during 1930—34 61 7 per cent during 1935—39 51 7 per cent during 1940—44 56.8 per cent during 1945—49 and 67 1 per cent during 1950—54. The probable group consisted of 30.3 per cent in the beginning of the period and 22.7 per cent at the end. The corresponding values for the suspected group were 14 3 and 10 2 per cent.

SEX DISTRIBUTION

Of 1 695 cases 1 085 were females (64 0 per cent) and 610 males (36.0 per cent) No difference was found with sex regard ing the distribution of the cases according to firmness of diagnosis — group A 1 contained 58 9 per cent and 56 7 per cent respectively for females and males group C-1 15 0 per cent and 18 0 per cent respectively Neither was any marked change or difference found between the sexes regarding distribution among the 5-year periods except that there was no increase during the War in the male group (military service?)

[1] Mean population of Malmö

largely on observations made at autopsy but in some reports it has been based on clinical data

Clinical series	*Mean age at death*	*Number of patients*
Contratto et al. (1937)	52 5	180
[illegible] et al. (1932)	65 0	30
Olesen et al. (1958)	55 5	30
Autopsy series		
K[illegible] et al (1947)	60 8	200
Lewes (1951)	63.6–72 2	25
Andersson et al. (1952)	63.2 – 64 2	45
Bergeron et al. (1954)	58 9	100
Mitchell et al. (1954)	65.3	63
Müller (1956)	73 5	112
Schmidt (1956)	56 – 62	45

The most important milestones in aortic stenosis as in mitral stenosis are age at time of rheumatic fever at time of first symptom at time of first attack of heart failure and at death In aortic stenosis there are however other well defined clinical phenomena such as the appearance of angina pectoris and syncope. Andersson et al. (1952) gave the survival after rheumatic fever with aortic stenosis as 13—62 years with a mean age of 35 6 years. The first symptoms of rheumatic heart disease in Olesen & Warburg's material appeared at 47.2 years and the mean survival was 8.8 years while angina pectoris (52 per cent of the entire material) appeared at a mean age of 50 7 years and the survival was 4 7 years on the average Cardiac failure occurred in 73.5 per cent in the above-mentioned series of Andersson et al. (1952) with a survival of a few days to 11 years with an average of 2.2 years. Bergeron et al. (1954) found that in pronounced stenosis in patients below 60 disability lasted only 1 month, against 4 7 years in patients above 60 and this was also found to hold for moderate stenosis when the corresponding figures were 7.5 months and 5.8 years.

The prognosis of aortic stenosis treated surgically has been described by Harken et al. (1959) and by Baker (1960). Since aortic stenosis was not operated upon at Malmö General Hospital during the period of investigation, this problem will not be discussed here

COMBINED VALVULAR LESIONS

The figures given above for the relative frequency sex distribution and prognosis are largely based on pure aortic or mitral lesions.

Mitral stenosis combined with aortic lesions was found to be equally common in males and females in Olesen's 1955 series and the frequency of those with rheumatic disease was 71 6 per cent. The mean age at the time of the first symptom which was 31.2 years did not differ from that for mitral stenosis and the mean age at the time of right heart failure was the same (45.6 years). Olesen sums up his impressions and says that mitral stenosis in combination with aortic disease differs but slightly regarding the course of the disease from pure mitral stenosis with the exception that survival from auricular fibrillation and right heart failure is shorter

Mitchell et al. (1954) reported a mean age at death of 65.3 years for pure aortic stenosis 52.5 for aortic stenosis and incompetence 48.4 for mitral and aortic stenosis and 36.5 for trivalvular stenosis. The mean survival after onset of congestive heart failure was 22.7 months for pure aortic stenosis 58.4 months for aortic and mitral stenosis and 80 months for trivalvular stenosis. For those patients who had had rheumatic fever the survival after the first attack was 47 6 years for pure aortic stenosis 28.2 years for mitral and aortic stenosis and 14 6 years for aortic mitral and tricuspid stenosis.

In his autopsy series from Oslo Müller (1956) found on comparison between cases from the years 1923—37 and 1943—47 that the mean age at death of patients with pure aortic stenosis was 68.5 years and 73.5 years respectively for the period of investigation, for pure mitral stenosis

Table 12. Total population and incidence of rheumatic heart disease per 5-year period in females grouped according to age

Total number of cases 1 113.

Period \ Age	0—9	10—19	20—29	30—39	40—49	50—59	≧60	Standardised morbidity rate
1930—34	7,674 *11* (1.4)	11,057 *20* (1.8)	15,868 *42* (2.7)	13,116 *30* (2.3)	10,637 *48* (4.5)	8,997 *29* (3.2)	8,582 *21* (2.5)	263.6
1935—39	8,900 *5* (0.6)	10,289 *13* (1.3)	16,262 *32* (2.0)	15,500 *32* (2.1)	11,651 *46* (4.0)	9,754 *31* (3.2)	10,492 *47* (4.5)	237.4
1940—44	12,466 *8* (0.6)	9,303 *21* (2.3)	15,643 *32* (2.1)	16,725 *51* (3.1)	13,420 *48* (3.6)	10,467 *42* (4.0)	12,812 *55* (4.3)	289.4
1945—49	16,452 *19* (1.2)	10,290 *13* (1.3)	15,417 *23* (1.5)	17,200 *34* (2.0)	15,969 *49* (3.1)	11,619 *52* (4.5)	15,138 *72* (4.8)	265.
1950—54	15,074 *9* (0.6)	13,895 *4* (0.3)	13,960 *10* (0.7)	17,455 *29* (1.7)	17,468 *43* (2.5)	13,569 *42* (3.1)	17,731 *50* (2.8)	171.3

Figures in first row indicate number of inhabitants in Malmö.
Figures in italics indicate number of cases of rheumatic heart disease.
Figures in brackets indicate number of cases of rheumatic heart disease per 1,000 inhabitants.

Table 13. Total population and incidence of rheumatic heart disease per 5-year period in males grouped according to age.

Total number of cases 627

Period \ Age	0—9	10—19	20—29	30—39	40—49	50—59	≧60	Standardised morbidity rate
1930—34	8,021 *12* (1.5)	10,460 *27* (2.6)	13,097 *20* (1.5)	11,426 *18* (1.6)	8,992 *17* (1.9)	7,519 *15* (2.0)	6,214 *12* (1.9)	151.3
1935—39	9,294 *3* (0.3)	9,614 *13* (1.4)	13,693 *16* (1.2)	13,767 *16* (1.2)	10,038 *24* (2.4)	8,220 *23* (2.8)	7,819 *11* (1.4)	147.2
1940—44	13,035 7 (0.5)	8,842 *19* (2.2)	13,192 *19* (1.4)	16,051 *19* (1.3)	11,720 *17* (1.5)	8,593 *13* (1.5)	9,779 *32* (3.3)	162.1
1945—49	15,948 *19* (1.2)	10,128 *9* (0.9)	13,923 *12* (0.9)	16,210 *21* (1.3)	14,185 *37* (2.6)	9,721 *29* (3.0)	11,398 *34* (3.0)	179.5
1950—54	15,054 *6* (0.4)	14,107 *9* (0.6)	13,003 *6* (0.5)	16,278 *17* (1.0)	15,882 *20* (1.3)	11,742 *17* (1.5)	13,335 *38* (2.9)	112.7

Figures in first row indicate number of inhabitants in Malmö.
Figures in italics indicate number of cases of rheumatic heart disease.
Figures in brackets indicate number of cases of rheumatic heart disease per 1,000 inhabitants.

RHEUMATIC HEART DISEASE

PRESENT MATERIAL

During the years 1930—54 1,371 patients with the diagnosis of mitral and/or aortic valvular disease and 369 patients with the diagnosis of non-specified valvular heart disease were admitted to the departments of medicine orthopædic surgery infectious diseases and pædiatrics of Malmö General Hospital. All patients were included whether the diagnosis was with a question-mark or not. Patients who were not residents of Malmö at the time of admission as well as patients with a firm or doubtful diagnosis of congenital heart disease and patients with syphilitic aortic lesions were excluded. In all cases the diagnoses refer to the first admission with the exception of the group with both mitral and aortic lesions, which consists of patients who on some occasion during the period covered by the present investigation, had had both conditions, no matter whether on first admission or later. In the description of this material any later revision of the diagnosis is ignored.

The distribution of the various groups of diagnoses — mitral, mitral and aortic, aortic and non-specified valvular lesions — is given below.

Valvular lesions

	Mitral	Mitral and aortic	Aortic	Non-specified	Total number of patients
Females	746	115	3.	21-	1 113
Males	2 1	87	117	152	627
Total	1 017	202	152	369	1 40

DISTRIBUTION OF DIFFERENT TYPES OF VALVULAR DISEASE

MITRAL LESIONS

During the 1930—54 period 1,20- patients were treated who on first admission had a diagnosis of mitral valvular disease and of whom 202 also had signs of aortic lesions on one occasion or another. 316 had a diagnosis of M.S. 483 of M.S. M.I. and 208 of M.I.

It is apparent from the figures given above that the number of diagnoses with a question-mark was highest in patients with the diagnosis of mitral incompetence 22.5 per cent for females and 15.. per cent for males. In patients with a diagnosis of mitral stenosis with or without incompetence the corresponding figures varied between 3 and 13 per cent.

The distribution per 5-year period is apparent from Figs. 20 and 21. The diagno-

The standardised morbidity rate (See page 14) given to the right in the Tables 12 and 13 shows that the frequency of females was highest during the 1940—44 period *after which it tended to decrease* —263.6—257.4—*289.4*—265 —171.3— and the males showed a similar tendency —184.3—147.2—162.1—*179.5* and 112.7 There was a distinct increase during the 40ies for both females and males, but this rise was much less pronounced if only those cases be considered in which the diagnosis had been firm, *i.e.* group A 1

Tables 12 and 13 also show the distribution of cases with a diagnosis of R H D with due allowance for changes in the population of the town during the period covered by the investigation. It is clear that the frequency of cases with a diagnosis of R.H.D between the ages of 10 and 39 years decreased for both females and males during the last three 5-year periods. A shift towards higher ages could also be noted for males in ages above 50 years but no such shift could be noted for the females.

AGE DISTRIBUTION

The age distribution at the time of first admission of the patients with a diagnosis of varying firmness is given in Figs. 30 and 31 Many patients were 40—49 years of age but a fair number of those with a firm diagnosis were above this age — namely 411 as against 326 below The distribution of the probable and suspected cases is noteworthy in that the frequency of these diagnoses in the lower age classes is high. The 0—9 age group included *38* suspected *40* probable and *9* certain cases and the 10—19 year age group 30 suspected 65 probable and 41 certain cases. The frequency of the cases with a firm diagnosis *increased from about 10 per cent in the* 0—9 year group to 70 per cent in the 40—49 year group after which it fell to about 60 per cent The number of cases with a probable or suspected diagnosis was distributed evenly among the different age classes.

FREQUENCY OF THE DIAGNOSIS OF RIGHT HEART FAILURE

It may be objected that the indications for admission changed during the period covered by the investigation and that this might explain the decrease in frequency during the last 5-year period and that an increasing number of patients were treated at the outpatient department. On the other hand a widening of the indications for admission might have occurred and resulted in the decrease in the frequency being larger than that suggested by the numerical values.

Even if the definition (see p. 96) of right heart failure is difficult and even if the criteria might have changed in the course of years — though reading of the record sheets did not leave any such impression — the frequency of this diagnosis may provide a yardstick of the severity of the valvular diseases in the hospitalised patients. The distribution per cent of the diagnosis of right heart failure among the 5-year periods for the entire material of 1 740 cases is given in p 83.

In patients with a firm diagnosis of valvular disease — group A 1 — the

Standardised morbidity rate

Firm diagnosis of rheumatic heart disease — Group A 1

Period	1930—34	1935—39	1940—44	1945—49	1950—54
Females	138.7	[illegible]	141.5	153.1	112.7
Males	92.6	78.7	81.0	*94.2*	73.8

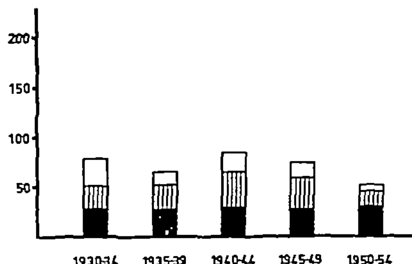


Fig. 21 *Rheumatic heart disease*

Distribution of mitral lesions in males on first admission during 1930—54.

Total number of cases 332.

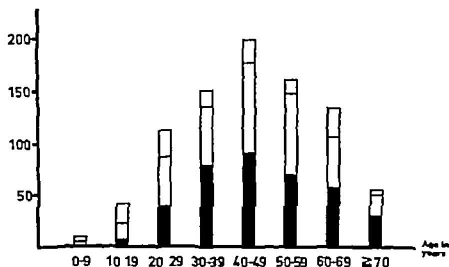


Fig. 22 *Rheumatic heart disease*

Age distribution of mitral lesions in females on first admission during 1930—54.

Total number of cases 855.

Stenosis — Stenosis and incompetence — Incompetence

Number of re-admissions within same 5-year period of admission for rheumatic heart disease

	1930—34	1935—39	1940—44	1945—49	1950—54
Females	1 4	1 6	1 4	1.5	1.6
Males	1.3	1.5	1 7	2.3	1 8

decreased. Thus even after this analysis there is reason to assume that a decrease would have been demonstrable in the frequency of rheumatic valvular lesions, if the number of admissions had not increased i.e. wider range of indications for hospitalisation.

NUMBER OF ADMISSIONS

The number of admissions of patients who had had a firm diagnosis of rheumatic heart disease — group A 1 — and who died within the 5-year period in which they were admitted for the first time is given above

It is clear that the number of admissions for females did not vary appreciably during the 25-year period apart from a possible slight increase in the 50ies compared with the 40ies. For the males the frequency of hospitalisation was high during 1945—49 but that was because a few patients were admitted on 6 or more occasions during that 5-year period. There was thus no evidence that the number of admissions increased to any appreciable extent during the 25-year period covered by the present investigation. Since this analysis covers all the deaths per 5-year period thus also those patients who died outside the hospital, it was possible to ascertain whether there was any difference between the groups that died in hospital and this afore-mentioned group It was found that the number of admissions for those in whom autopsy had revealed valvular lesions was 1 6 for the females and 1 9 for the males. For those who died in hospital but who were not autopsied, the corresponding figures were 1 6 and 1.6 and for those who died outside the hospital 1.3 and 1 6, respectively The number of admissions was thus somewhat lower for this last mentioned group. The numbers of admissions are in good agreement with those given by KUMPE & BEAN (1948) for aortic stenosis, namely 1 4 (mild lesions 1.87 and severe 1.34)

COMMENTS

The analysis of the series of rheumatic heart disease showed that the total number of patients with valvular disease had not decreased but, remained largely unchanged up to 1950 and then decreased. With due allowance for changes in the number of the population the standardised morbidity rate will show the highest figure for the 1940—44 period for females and for the 1945—49 period for males. Military service during the War and care in military hospitals can probably explain this distribution and the figures from the years 1945—53 from military archives (*Försvarets Sjukvårdsstyrelse*) showed the highest frequency of recruits rejected because of R.H.D in 1945 Since the figures are based on the entire material irrespective of the firmness of the diagnosis, the series was divided into 3 groups according to the firmness of the diagnosis: group A 1 firm diagnosis of R.H D group B-1 probable and group C-1 suspected. The figures for all groups, A 1 B-1 and C-1 showed a frequency of 4.2—4 9 per 10 000 per year up to 1950 after which it fell to 3.0 As far as group A 1 is concerned the frequency per 10,000 inhabitants was practically unchanged up to 1950 after ... ignificantly from 2.6 ... 0 inh ... ts per

	A.S.	A.S. A.I.	A.I.	Total number patients
emales	12 (2)	13 (0)	10 (1)	33 (3)
ales	39 (1)	36 (3)	42 (0)	11" (4)
otal	1 (3)	49 (3)	2 (1)	1 2 (7)

(Figures in brackets indicate patients in whom diagnosis was with a question-mark)

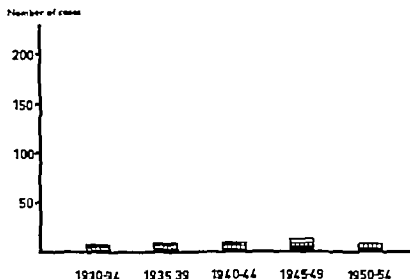


Fig. 24. *Rheumatic heart disease*
Distribution of pure aortic lesions in females on first admission during 1930—54.
Total number of cases 33.

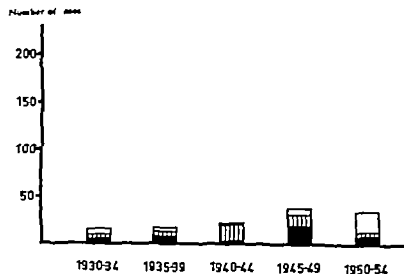


Fig. 25. *Rheumatic heart disease*
Distribution of pure aortic lesions in males on first admission during 1930—54.
Total number of cases 117

Stenosis | Stenosis and Incompetence | Incompetence

TRACING OF PATIENTS

The number of patients still alive on January 1 1958 was ascertained from a search of the parish registers.

PURE MITRAL LESIONS

746 females and 271 males had during 1930—54 had a diagnosis of pure mitral lesion at the first admission. 61 (8.2 per cent) females and 23 (8.5 per cent) males could not be traced mainly because of incomplete data in the hospital records.

MORTALITY

378 (50 7 per cent) females and 124 (45.8 per cent) males had died in the meantime The distribution of these patients according to the time of their first admission to the hospital during the investigation period is apparent from

Table 14 Survey of the series of pure mitral valvular disease
Females.

	1930—34	1935—39	1940—44	1945—49	1950—54	Total
Number of cases	138	134	171	172	131	746
Group A	87 (63.0)	88 (65.7)	92 (53.8)	112 (65.1)	91 (69.5)	470 (63.0)
Group B	38 (27.5)	33 (24.6)	44 (25.7)	38 (22.1)	30 (22.9)	183 (24.6)
Group C	10 (7.2)	11 (8.2)	31 (18.1)	17 (9.9)	8 (6.1)	77 (10.3)
No clinical data	3 (2.2)	2 (1.5)	4 (2.3)	5 (2.9)	2 (1.5)	16 (2.1)
Follow-up 1958						
Deaths	77 (55.8)	84 (62.7)	78 (45.6)	89 (51 7)	50 (38.2)	378 (50.7)
Not traced	27 (19 6)	11 (8.2)	16 (9.4)	7 (4.1)	—	61 (8.2)
Survivors						
Examined	25 (18.1)	20 (14.9)	54 (31 6)	48 (27 9)	34 (26 0)	181 (24.3)
Not examined	9 (6.5)	19 (14.2)	23 (13.5)	28 (16.3)	47 (35.9)	126 (16.9)

(Figures in brackets indicate percentages)

Table 15 Survey of the series of pure mitral valvular disease
Males.

	1930—34	1935—39	1940—44	1945—49	1950—54	Total
Number of cases	61	42	65	59	44	271
Group A	31 (50.8)	24 (57 1)	32 (49.2)	30 (50.8)	30 (68.2)	147 (54.2)
Group B	20 (32.8)	10 (23.8)	15 (23.1)	10 (16.9)	9 (20.5)	64 (23 6)
Group C	9 (14 8)	6 (14.3)	18 (27 7)	16 (27 1)	2 (4.5)	51 (18.8)
No clinical data	1 (1 6)	2 (4.8)	—	3 (5.1)	3 (6.8)	9 (3.3)
Follow-up 1958						
Deaths	30 (49.2)	23 (54.8)	26 (40.0)	26 (44 1)	19 (43.2)	124 (45 8)
Not traced	13 (21.3)	6 (14.3)	2 (3.1)	—	2 (4.5)	23 (8.5)
Survivors						
Examined	9 (14.8)	9 (21 4)	22 (33.8)	25 (42.4)	4 (9 1)	69 (25.5)
Not examined	9 (14 8)	4 (9.5)	15 (23.0)	8 (13 6)	19 (43.2)	55 (20.3)

(Figures in brackets indicate percentages)

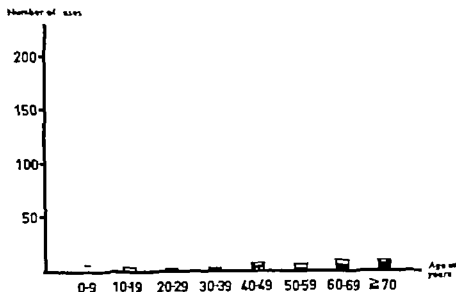


Fig. 26 *Rheumatic heart disease*

Age distribution of pure aortic lesions in females on first admission during 1930—34

Total number of cases 33.

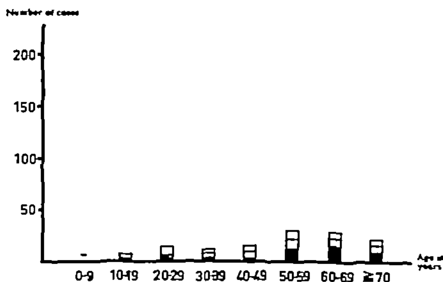


Fig. 27 *Rheumatic heart disease*

Age distribution of pure aortic lesions in males on first admission during 1930—34

Total number of cases 117

Stenosis   Stenosis and Incompetence   Incompetence

MORTALITY

73 (63.5 per cent) females and 56 (64.4 per cent) males had died during the period 1930—58. The distribution of these patients according to time of first admission to the hospital during the investigation period is apparent from Tables 17 and 18.

15 of the aforementioned females had died outside the hospital, 58 in the hospital and of those 48 (82.8 per cent) had been autopsied. 16 males had died outside the hospital 40 in the hospital and of those 31 (77.5 per cent) had been autopsied. Of group A 1 — firm diagnosis — 63 (54.8 per cent) out of 115 females had died and 44 (69.8 per cent) had been autopsied, and 49 (56.3 per cent) out of 87 males had died and 27 (55.1 per cent) had been autopsied

RESULTS OF THE RE-EXAMINATION

16 females and 14 males were re-examined in the 1953 or 1955—58 period, representing 13.9 and 16.1 per cent of the

Table 17 Survey of the series of combined mitral and aortic valvular disease
Females.

	1930—34	1935—39	1940—44	1945—49	1950—54	Total
Number of cases	21	24	31	18	21	115
Group A	18 (85.7)	21 (87.5)	24 (77.4)	15 (83.3)	19 (90.5)	97 (84.3)
Group B	2 (9.5)	2 (8.3)	6 (19.4)	2 (11.1)	—	12 (10.5)
Group C	1 (4.8)	—	1 (3.2)	—	2 (9.5)	4 (3.5)
No clinical data	—	1 (4.2)	—	1 (5.6)	—	2 (1.7)
Follow-up 1958						
Deaths	14 (66.7)	19 (79.2)	19 (61.3)	14 (77.8)	7 (33.3)	73 (63.5)
Not traced	4 (19.0)	—	2 (6.5)	2 (11.1)	1 (4.8)	9 (7.8)
Survivors						
Examined	2 (9.5)	3 (12.5)	8 (25.8)	2 (11.1)	1 (4.8)	16 (13.9)
Not examined	*1 (4.8)*	*2 (8.3)*	*2 (6.5)*	—	*12 (57.1)*	*17 (14.8)*

(Figures in brackets indicate percentages)

Table 18. Survey of the series of combined mitral and aortic valvular disease
Males.

	1930—34	1935—39	1940—44	1945—49	1950—54	Total
Number of cases	17	25	19	17	9	87
Group A	16 (94.1)	21 (84.0)	16 (84.2)	15 (88.2)	8 (88.9)	76 (87.4)
Group B	—	—	—	—	—	—
Group C	1 (5.9)	4 (16.0)	2 (10.5)	2 (11.8)	1 (11.1)	10 (11.5)
No clinical data	—	—	1 (5.3)	—	—	1 (1.1)
Follow-up 1958						
Deaths	7 (41.2)	17 (68.0)	12 (63.2)	13 (76.5)	7 (77.8)	56 (64.4)
Not traced	5 (29.4)	3 (12.0)	2 (10.5)	—	—	10 (11.5)
Survivors						
Examined	4 (23.5)	4 (16.0)	4 (21.1)	1 (5.9)	1 (11.1)	14 (16.1)
Not examined	1 (5.9)	1 (4.0)	1 (5.3)	3 (17.6)	1 (11.1)	7 (8.0)

(Figures in brackets indicat percentages)

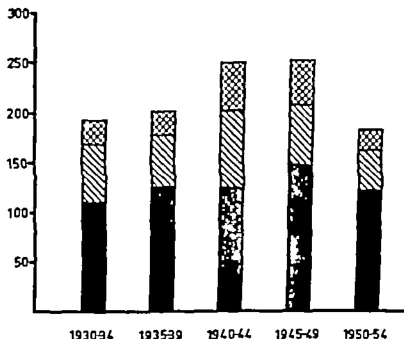


Fig. 28. *Rheumatic heart disease.*
Classification of females according to firmness of diagnosis.
Total number of cases 1,085.

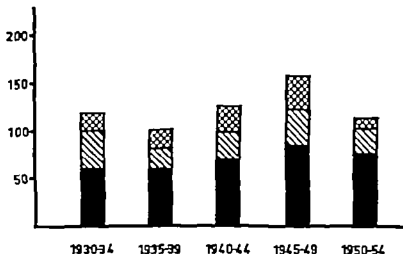


Fig. 29. *Rheumatic heart disease.*
Classification of males according to firmness of diagnosis.
Total number of cases 610.

Firm   Probable   Suspected

afore-mentioned females had died outside the hospital, 17 in the hospital and of those 15 (88.2 per cent) had been autopsied. 21 males had died outside the hospital, 57 in the hospital and 50 (87 7 per cent) of these had been autopsied. Of group A 1 — firm diagnosis of R.H.D — 15 (60 0 per cent) out of 25 females had died and 11 (73.3 per cent) had been autopsied and 58 (64 4 per cent) out of 90 males had died, and 44 (75 9 per cent) had been autopsied.

RESULTS OF THE RE-EXAMINATION

Of 4 patients with a diagnosis of aortic stenosis on first admission, the diagnosis was confirmed in 2 and was excluded in 2. Of 8 patients with a diagnosis of aortic stenosis with incompetence the diagnosis was confirmed in 7 and excluded in 1

NON-SPECIFIED VALVULAR LESIONS

217 females and 152 males had during 1930—54 had a diagnosis of "non-specified valvular lesions on first admission. 15 (6 9 per cent) females and 21 (13.8 per cent) males could not be traced, mainly because of incomplete data in the hospital records.

MORTALITY

73 (33.6 per cent) females and 45 (29 6 per cent) males had died in the meantime. The distribution of these patients according to the time of their first admission to the hospital during the investigation period is apparent from Tables 21 and 22. 33 of the above-mentioned females had died outside the hospital, 40 in the hospital and of those 25 (62.5 per cent) had been autopsied. 16 males had died outside the hospital, 29 in the hospital and 24 (82.8 per cent) had been autopsied Of group A 1 — firm diagnosis of R.H D — 23 (50 0 per cent) out of 46 females had died and 25 had been autopsied and 20 (60 6 per cent) out of 33 males had died and 16 had been autopsied

RESULTS OF THE RE-EXAMINATION

67 females and 34 males were re-examined in 1953 or in the 1955—58 period, representing 30 9 and 22.4 per cent of the total group respectively and 51 9 and 30.5 per cent of those who were still alive and could be traced in 1958.

In 37 (55.2 per cent) females and 20 (58.8 per cent) males with a diagnosis of non-specified valvular lesion at the first admission, the diagnosis was excluded at the re-examination. The distribution of certain R.H.D among females and males showed a frequency of 23.9 per cent and 17 7 per cent, respectively

COMMENTS

This survey of the material is concerned with data on the number and frequency of deaths patients not traced or examined during the observation period of 3—28 years and secondly with the results of the re-examination during the 50ies. The mortality in the respective groups was high. for mitral stenosis it was 50 per cent, for mitral and aortic lesions it was 60 per cent, and for aortic lesions only it was 70 per cent while for the non-specified group it was as low as about 30 per cent. The number of patients not traced was about 10 per cent, mainly from the 1930—39 period.

The results of the re-examination may at first glance appear bewildering in that previous diagnoses of R.H D could be excluded. Though it is not intended to discuss why the diagnosis could often not be confirmed it might be mentioned that most of the cases diagnosed during the 1930—50 period were signed by Professor Ljungdahl so that there is no reason to doubt the correctness of the auscultatory findings. The diagnoses refer to the first admission during the period covered by the investigation, and in some cases the diagnosis had a question-mark and in some there was co-existent A.R.F The commonest conditions in which an incorrect diagnosis of R.H.D is liable to be

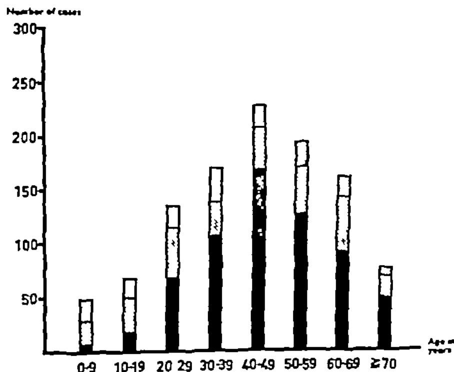


Fig. 30 *Rheumatic heart disease*
Cla sification of females accordi g to age and firmness of diagnosis.
T tal number of cases 1 085.

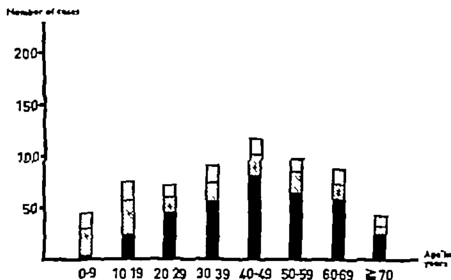


Fig. 31. *Rheumatic heart disease*
Classification of males according to age and firmness of diagnosis.
T tal number of cases 610.

DISTRIBUTION OF VALVULAR LESIONS IN A CLINICAL AND AN AUTOPSY SERIES

The clinical series of valvular disease consists of 229 patients re-examined in 1953 and admitted to hospital during the period 1930—50 and the autopsy series consists of 463 patients who died and were examined post-mortem during the period 1930—58.

There was a certain overlapping between the groups in that 26 patients examined in 1953 had died and been autopsied in 1955—58. However this will not influence any conclusions that might be drawn from the series.

The distribution of the different types of valvular lesions is given in Table 23. A detailed comparison between the various types of valvular disease in a clinical series and in an autopsy series is hardly possible because the diagnoses in the two series are based on different findings but a certain idea of the reliability of the firmness of the clinical diagnosis can be deduced. The diagnosis of valvular lesions in the autopsy series was based on a thickening and a fusion of valves and those cases in which post mortem examination showed only slight valvular changes are not included. Here a diagnosis of incompetence is to be understood as a dilatation of the ostium, stenosis with incompetence, as a slight narrowing; and stenosis as a marked narrowing.

No exact data were given on the size of the ostia in all of the record sheets and thus a more detailed division is not possible.

It is clear from Table 23 that of 463 autopsied patients 259 (55.9 per cent) had only mitral disease and the corresponding number for the clinical series was

Table 23. *Distribution of valvular lesions.*

	Autopsy series				Clinical series			
	F	M	Total		F	M	Total	
M	166	57	223		67	18	85	
MS MI	16	11	27	(55.9)	38	6	44	(58.5)
MI	4	5	9		2	3	5	
AS	18	41	59		—	1	1	
AS AI	1	—	1	(16.4)	3	9	12	(17.5)
AI	3	13	16		10	17	27	
MS AS	27	18	45		1	—	1	
MS AS AI	26	10	36		3	1	4	
MS AI	1	—	1		18	10	28	
MS MI AS	5	11	16	(24.2)	—	—	—	(24.0)
MS MI AI	—	2	2		15	4	19	
MS MI AS AI	2	5	7		2	1	3	
MI AS	—	4	4		—	—	—	
MI AI	—	1	1		—	—	—	
M and or A and or Tri and or P	15	1	16	(3.5)	—	—	—	
Total	284	179	463		159	70	229	

(Figures in brackets indicate percentages)

Frequency of the diagnosis of heart failure in rheumatic heart disease

Period	1930—34	1935—39	1940—44	1945—49	1950—54
Females	14 4	20 4	22.2	24 1	19 8
Males	10 0	22.6	23.8	23 0	15.9

(The figures indicate percent ges)

tendency will be th sam with the lowest frequency figures in the beginning and the end of the period For the female group with the diagnosis of mitral stenosi with or without incompetence in group A 1 the distribution was 13.. 19 4 23.2—23.3—15 8 per cent and for males 13 4—15 1—20.2—22 4—20.0 per cent per 5-year period. The difference between the 2 last mentioned 5-year periods is almost significant for the females ($P<0.05$) while the decrease in frequency from 1940—44 to 1950—54 was not significant for the males.

COMMENTS

Thus the frequency f heart failure was lowest during the first nd th last 5-year periods. The low frequency in the beginning of the period is probably due to a low frequency f hospitalisation rather than to the patients having been less seriously ill during that period which is apparent from th fact that from 1930 to 1935 the number of patient who died in hospital increased namely from 24 per cent to 32 per cent f th pop lati n in th area served by the hospital (See population data) The low frequency during the last 5-year period may be explained in many ways, such as improved therapeutic possibilities increased number of cases referred f r investigation etc. Another explanation is that in the begin ning of the bservation period more pati nts with R H.D were admitted because of A.R.F than at the end (page 25).

Th frequency of the diagnosis of heart failure suggests that the decrease observed during the last 5-year period in the hospi talised patients would have been larger if the rang f indications had not been widened t include less serio s cases.

MORTALITY

The mortality in the material should provide a measure f the indications for admission and in the following table the frequency is given of those patients who died during the same 5-year period during whi h they were first admitted to hospital. The figures apply to all cases in groups A 1 B-1 and C 1

Since the mortality proved highest in group A 1 — 50 4 per cent as against 28.7 per cent in group B-1 and 32.7 per cent in group C-1 — and since the last 5-year period contains a higher percentage of group A 1 the figures will be too low for the periods during the 30ies and 40ies and there is reason t believe that the mortality during the last 5-year period

Mort lity within same 5-year period of admission for rheumatic heart disease

Period	1930—34	1935—39	1940—44	1945—49	1950—54
Females	28.4	43.2	30 4	38 6	31 6
Males	39.7	32.1	38.9	38.5	38 1

(The figures indicate percentages)

had systolic murmurs and all had normal blood pressures except one

Of the 16 patients, who were submitted to a more thorough examination all had systolic murmurs (13 with a basal systolic and 3 with an apical systolic murmur) and one had an aortic diastolic murmur. Blood pressure was normal in 12 and increased in 4 only one patient had a low blood pressure (100/70 mm Hg). The electrocardiograms showed sinus rhythm in 15 and bigeminy in 1 left bundle branch block in 4 right bundle branch block in 1 left ventricular hypertrophy in 9 and no abnormal signs in 2. All 6 patients examined roentgenographically showed enlargement of the left half of the heart. No special search was made for calcification of the aortic valves. The afore-mentioned 21 cases were distributed evenly among the 5-year periods.

In view of the above findings there is reason to believe that if the examiner had considered the possibility of aortic stenosis also in the higher age classes the diagnosis would probably have been made clinically

THE NATURAL HISTORY OF RHEUMATIC HEART DISEASE

The natural history of R.H.D is outlined and discussed below on the basis of the observation made in the clinical and autopsy series. The description is based largely on five factors namely mean age at the time of first attack of A.R.F mean age at the time of diagnosis mean age at the time of first heart symptoms, mean age at the time of right heart failure and at death.

Tables 24 and 25 give these milestones for some of the groups in the autopsy series while 40 of the entire group of 403 will not be accounted for. This small group includes a combination of mitral stenosis and or mitral incompetence and or other valvular lesions. No more or less homogenous group could be discerned.

The analysis showed that the prognosis of all valvular lesions was very good and in females the mean age at death was above 50 years for all groups. This compares favourably with figures given in the literatur This might in some measure be explained b the fact that the values are based on an autopsy m terial and therefore a few data will be given from the clinical series.

ACUTE RHEUMATIC FEVER

The low frequency of a firm diagnosi f A.R.F in the history of patients with mitral stenosis in the autopsy series may be ascribed to the high frequency of probable A.R.F in this group. Of 166 females 28 (16.9 per cent) had had a probable A.R.F and the corresponding figures for males were 57 and 8 (14.0 per cent). The frequency of probable A.R.F among females was in the group with

M.S.A.S.	14.8 per cent
M.S.A.S.A.I.	18.5 per cent
M.S M.I. (M.I.)	20 0 per cent
A.S.	5 6 per cent
A.S.A.I. (A.I.)	0 0 per cent

The corresponding figures for the males were in the group with

M S.A.S	11.2 per cent
M.S.A S.A I	10 0 per cent
M S M.I (M.I)	12.5 per cent
A.S	7.3 per cent
A.S.A.I (A.I)	7 7 per cent

Firm or probable A.R.F occurred in 50—60 per cent of the total material.

The mean age at the time of first attack was higher for females than for males (17 7 and 15 6 respectively) which is in good agreement with the figures of OLERUD (1955), who gave 16.3 and 14 0 years respectively. The mean age at time of first attack was thus somewhat lower than in the present material.

Predicted frequency of rheumatic heart disease per 10 000 inhabitant in the future as calculated from the frequency of acute rheumatic fever during 1930—34

	A.R.F		R.H.D		
	Firm	Probable	Firm	Probable	Calculated
1930—34	2.5	1.2	2.7	2.2	—
35—39	1.0	1.2	2.5	1.7	—
1940—44	1.8	1.3	2.1	2.3	—
45—49	1.3	1.7	2.0	2.0	—
1950—54	0	0.7	2.0	1.0	—
55—59	(0.)		(2.5)		1.8
1960—64					1.0
65—69					1.1
1970—74					0.9
75—9					0.5

year. There is no reason to believe that this decrease in frequency is due to an increasing percentage of patients being treated at the outpatient department because the number of patients with complicating cardiac failure at the time of the first admission and the mortality per 5-year period had most likely decreased during the last 5-year period. It is therefore probable that the range of indications for admission had been widened which sounds all the more probable because of an increased number admitted for preoperative observation.

Judging from the figures found for R.H.D. and A.R.F. it might be possible, all other factors being equal, to predict at least approximately what the frequency of R.H.D. might be in future. With knowledge of the survival rate from the first attack of A.R.F. to death (between 25 to 30 years on the average) it should be possible to deduce the frequency of R.H.D. and vice versa. An example is given below: The frequency of a firm diagnosis of A.R.F. during 1930—34 was 2.5/10,000 inhabitants per year and the frequency of R.H.D. in this group was 25 per cent or somewhat higher on account of a higher frequency of recurrences of A.R.F. during this period. This gives a R.H.D. frequency of 0.8/10 000 and to this figure must be added the frequency of R.H.D. in the probable group — 10 per cent of 1.2/10 000 — 0.1/10 000. With knowledge of the number of patients with R.H.D. with a history of A.R.F., in the present example 0.9/10,000 inhabitants it is possible to calculate the number without, which will be just as many (50 per cent). Thus 30 years later the incidence of R.H.D. will be 1.8/10 000 and the incidence during 1950—54 was 2.0/10 000 of firm diagnosis of R.H.D., and 1.0/10 000 of probable diagnosis.

The calculation is of course only approximate and will only hold if the frequency of A.R.F. in patients with R.H.D. remains constant, as it did during the 25-years covered by the present investigation. The expected frequency of R.H.D. per 10 000 inhabitants would be 1.8 about 1955—59 and the observed frequency for firm diagnosis during 1955—59 was about 1.8. Thus a good agreement. With reference to EDSTRÖM (1935) the frequency of A.R.F. in 1910—30 showed no substantial decrease during those years in Malmö and thus no decrease can be expected in the frequency of R.H.D. during 1930—50. This may explain why the frequency of R.H.D. for the years in the present investigation was largely constant.

Only 10.5 per cent of the patients were above 29 at the time of the first attack of A.R.F but in many of these R.H.D had been suspected before the first known attack of A.R.F

MEAN AGE AT THE TIME OF DIAGNOSIS OF RHEUMATIC HEART DISEASE

Assessment of the time of first diagnosis of R.H.D is impaired by the fact that some patients are unable to state exactly when the diagnosis was made. It is however a point of interest in the natural history of R.H.D The figures given in the tables shows that for patients in the autopsy series the mean age at the time of diagnosis was usually between 37 and 43 years but somewhat higher for patients with A.S. The mean age at the time of the diagnosis in the clinical series was 35 6 years.

A clinical diagnosis was made in 81 4 per cent of the autopsy series. In the series of EDSTROM et al. (1954) the corresponding figure was 73 per cent.

AGE AT ONSET OF HEART SYMPTOMS

Onset of symptoms is not to be understood as an attack of embolism or bacterial ndocarditis but as decreased working capacity In some cases symptoms persisted from the first attack of acute rheumatic fever but usually there was a free interval, after which symptoms appeared insidiously or in association with complicating diseases. The onset of symptoms implies function class II according to the N Y.H.A.s criteria.

The mean age at the time of first symptoms in the autopsy series was between 36 and 45 years with exception of the group with A.S. in which symptoms appeared at 58 years in females and at 53 years in males.

The mean age at the time of first heart symptoms was 42.8 years in the clinical series and *there was thus no appreciable difference between the clinical and the autopsy series* The mean age at the time of first symptoms in the females was 45 3 years and in the males 41 4

While symptoms of heart disease in the autopsy series had been noted in 80 per cent or more in the different groups, only half of the group with M.S.M.I.(M.I) had had symptoms.

RIGHT HEART FAILURE

Right heart failure is to be understood as present when such signs as enlargement of the liver ascites oedema increased venous pressure are demonstrable. Leg oedema alone was not regarded as a sign

Age at first heart symptoms in the autopsy series

Mitral stenosis

Age	<20	20—20	30—39	40—49	50—59	≥60	Total
Number of pati nt	8	20	52	36	43	34	193
Per cent	4 2	10 4	26.9	18.7	22.3	17 6	100 1

Aortic stenosis

Age	40	40—49	50— 9	60—69	≥70	Total
Number of patient	7	6	12	13	9	47
Per cent	14 9	12.8	2 .5	27 7	19 2	100 1

Table 16 Result [illegible] xamina[illegible]

Diagnosis on first admission	Sex	R H D Rheumatic heart disease			Total
		Certain	Uncertain	Excluded	
M.S.		4[illegible] ( )	5 (7[illegible]	17 (23.9)	71
		[illegible] (3[illegible])	6 (2[illegible])	15 (50.0)	30
M.S. M.I.		47 (63[illegible])	13 (1[illegible] 6)	14 (18 9)	74
		11 (4[illegible] 8)	2 (8.7)	10 (43.[illegible])	23
M I.		16 (44 4)	7 (19 4)	13 (36.1)	36
		3 (18 8)	3 (18 8)	10 (62.5)	16

(Figures [illegible] brackets indicat[illegible] percentages)

Tables 14 and 15. 114 of the above m[illegible]n tioned females had died outside the h[illegible]spital 264 in the hospital and [illegible]f those 220 (86.7 per cent) had been autopsied 29 males had died outsid[illegible] the hospital, 95 in the hospital and of those 82 (86.3 per cent) had been autopsied.

Of group A 1 [illegible] firm diagnosis of R.H D — 288 (60 9 per cent) out of 470 females had died 207 (44 0 per cent) had been autopsied, [illegible]nd 90 (61.2 per cent) out of 147 males had died and 73 (49 7 per cent) had been autopsied.

RESULTS OF THE RE-EXAMINATION

181 females and 69 males were re-examined in the 1953 [illegible]r 1955—58 period representing 24.3 and 25.5 pe[illegible] cent of the total group respectivel[illegible] and 59 0 and 55.7 per cent [illegible]f those who were still [illegible]live and could be traced in 1958

MITRAL STENOSIS

Table 16 [illegible]hows that [illegible] 17 (23.9 per cent) of the females with a diagnosis of mitral stenosis [illegible]n first admissio[illegible] the diagno[illegible]is was excluded at the re-examination. The corresponding figures for males were 15 (50 0 per cent). The distribution of certain R.H D among females and males showed a frequency of 69 0 per cent and 30 0 per cent respectively

MITRAL STENOSIS WITH INCOMPETENCE

Tabl[illegible] 16 also shows that similar figures were found for patients who at first admission had a diagnosis of mitral stenosis with incompetence

MITRAL INCOMPETENCE

Table 16 shows that in 13 (36.1 per cent) of the females with a diagnosis of mitral incompetence at the first admission, the diagnosis was excluded at the re-examina[illegible]tion Th[illegible] corresponding figures for males were 10 (62.5 per cent). Th[illegible] distribution of certain R.H D among [illegible]f males and males showed a frequency of 44 4 per cent and 18.8 per cent respectivel[illegible]

COMBINED MITRAL AND AORTIC LESIONS

115 females and 87 males had during 1930—54 had a diagnosis of combined mitral and aortic lesions at the first admission. 9 (7.8 per cent) females and 10 (11.5 per cent) males could not be traced, mainly because [illegible]f incomplete data in the hospital records.

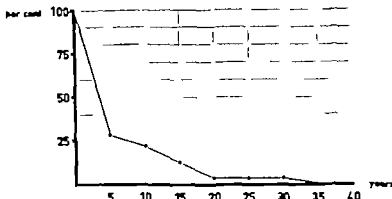


Fig. 32. *Aortic stenosis.*
Survival after onset of heart symptoms.
Females and males. Total number of cases 46.

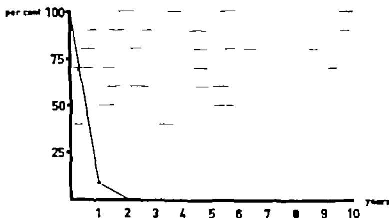


Fig. 33. *Aortic stenosis.*
Survival after first attack of right heart failure.
Females and males. Total number of cases 36.

AORTIC STENOSIS

The prognosis of M.S will be discussed further (see page 109) and here only the prognosis of patients with A.S will briefly be dwelt on. Fig. 32 shows the survival of patients with A.S in the autopsy series for 46 patients from the time of first heart symptoms and Fig. 33 shows the survival from first attack of right heart failure. The prognosis in A S has not changed during the investigation period.

Already 5 years after the first symptoms 70 per cent had died and after 20 years only 4 per cent are still living. After the first attack of right heart failure the prognosis was very bad with a survival of less than 10 per cent after one year. This is in good agreement with the survival rate described in the literature (WILLIUS 1927 ANDERSSON et al. 1952, BERGERON et al. 1954 OLESEN & WARBURG 1958)

total groups, respectively and 18.5 per cent and 66.7 per cent of those who were still alive and could be traced in 1958. In 24 patients the diagnosis of certain R.H.D was confirmed and in 5 it was excluded. In only one patient the diagnosis was uncertain R.H D.

PURE AORTIC LESIONS

35 females and 117 males had during 1930—54 had a diagnosis of pure aortic lesion on first admission. 4 (11 4 per cent) females and 6 (1 per cent) males could n t be traced mainly because of incompl t data in the hospital records.

MORTALITY

25 (71 4 per cent) females and 78 (66 7 per cent) m les had died in the meantime. Th distribution of these patients according to tim of th ir first admission to th hospital during the investigation is apparent from Tables 19 and 20. 8 of the

T ble 19. Survey of the series f pure aortic alvular disease.
Females.

	1930—34	1935—39	1940—44	1945—49	1950—54	Total
Number of cases	6	6	6	11	6	35
Group A	3 (50 0)	4 (66 7)	3 (50 0)	10 (90.9)	6 (100)	26 (74.3)
Group B	3 (50.0)	1 (16.7)	1 (16 7)	—	—	5 (14.3)
Group C	—	1 (16 7)	2 (33.3)	1 (9 1)	—	4 (11 4)
N clinical data	—			—	—	—
Follow-up 1958						
Deaths	3 (50.0)	6 (100.0)	3 (50.0)	9 (81 8)	4 (66 7)	25 (71 4)
Not traced	1 (16.7)	—	2 (33.3)	—	—	3 (8 6)
Survivors						
Examined	2 (33 3)	—	1 (16.7)	1 (9 1)	1 (16.7)	5 (14.3)
Not examined	—	—	—	1 (9 1)	1 (16.7)	2 (5.7)

(Figures in brackets indicat percentages)

Table 20. Survey of the series of pure aortic val ular disease.
Males.

	1930—34	1935—39	1940—44	1945—49	1950—54	Total
Number f cases	14	15	20	35	33	117
Group A	10 (71 4)	10 (66.7)	15 (75 0)	28 (80.0)	27 (81.8)	90 (76 9)
Group B	2 (14.3)	2 (13.3)	3 (15.0)	4 (11 4)	3 (9 1)	14 (12.0)
Group C	2 (14.3)	3 (20 0)	1 (5.0)	3 (8.6)	3 (9.1)	12 (10.3)
N clinical data	—	—	1 (5.0)	—	—	1 (0 9)
Follow-up 1958						
Deaths	10 (71 4)	11 (73.3)	13 (65.0)	25 (71 4)	19 (57.6)	78 (66.7)
Not traced	2 (14.3)	1 (6.7)	2 (10.0)	—	1 (3.0)	6 (5.1)
Survivors						
Examined	1 (7 1)	1 (6.7)	3 (15.0)	8 (22.9)	3 (9 1)	16 (13.7)
Not examined	1 (7 1)	2 (13.3)	2 (10 0)	2 (5.7)	10 (30.3)	17 (14.5)

(Figures in brackets indicate percentages)

Mean age at death from rheumatic heart disease (excluding pure aortic stenosis)

	Autopsy series Acute rheumatic fever in history	
	with	without
1930—39	47.2 (33)	49 9 (38)
1940—49	49 4 (81)	55.5 (75)
1950—58	52.3 (49)	61 9 (49)

(Figures in brackets indicate the number of patients)

For females with M.S. in the autopsy series and with a firm diagnosis of A.R.F., the mean age at death during 1930—39 was 53.7 years during 1940—49 54 0 years and during 1950—58 56 2 years. The corresponding figures for females without A R F were 53.7 56 0 and 61 4 years.

For males with M.S. and with a firm diagnosis of A.R.F the mean age at death was 47 4 years during 1930—39 41 6 years during 1940—49 and 48.0 years during 1950—58 The corresponding figures for males with M.S and without A.R.F were 41 7 48 3 and 60 1 years The increase in the mean age at death in females and males with M.S. who had not had a clinical diagnosis of acute rheumatic fever was however statistically not significant.

It thus appears that the prognosis of R.H.D with A.R.F has not changed with certainty but the prognosis in R H.D without A.R F probably has and the same tendency holds for patients with mitral stenosis.

This might give reason to question whether R.H.D in the two groups is of the same aetiology The frequency of A.R.F in the autopsy series has not changed during the observation period and persisted at about 50 per cent throughout the observation period. The improvement in the prognosis of R H.D without A.R F can therefore hardly be ascribed to any reduction in the severity of A.R.F because otherwise the prognosis should be the same in both groups. If it still be assumed that both groups had had rheumatic fever when did the subclinical phase of A.R.F occur in the group with R.H D "without A.R.F? The mean age at onset of first heart symptoms in patients with M.S. with A.R.F was 44 1 years for females and 39 8 years for males in 1930—39 and 44 5 and 41.8 in 1950—58 respectively For females with M.S. without A R.F the figure for 1930—39 was 37.2, for 1940—49 41.3 and for 1950—58 51.3 years. The corresponding figures for males were 42.3 47.3 and 49.3 years. Can the subclinical attack have made its first appearance at increasingly higher age?

The difference between the prognosis of R.H.D with or without A.R.F gives rise to the question whether *all* rheumatic valvular lesions are of rheumatic origin. This question will perhaps be answered automatically in the future if and when the rheumatic heart disease has disappeared

Table 21 Survey f the series f non pecified valv lar di ase.
Females.

	1930—34	1935—39	1940—44	1945—49	1950—54	Total
Number of cases	36	42	49	61	29	217
Group A	4 (11 1)	15 (35)	7 (14.3)	13 (21 3)	7 (24 1)	46 (21.2)
Group B	17 (47.2)	16 (38.1)	24 (49 0)	22 (36.1)	11 (37.9)	90 (41.5)
Group C	12 (33.3)	9 (21 4)	16 (32)	24 (39.3)	10 (34 5)	1 (32.7)
No clinical data	3 (8.3)	2 (4 8)	2 (4 1)	2 (3 3)	1 (3.4)	10 (4.6)
Follow-up 1955						
Deaths	13 (36.1)	17 (40 5)	15 (30.6)	20 (32 8)	8 (27 6)	73 (33.6)
Not traced	4 (11 1)	7 (16.7)	2 (4.1)	1 (1.6)	1 (3.4)	15 (6 9)
Survivors						
Examined	7 (19 4)	10 (23 8)	20 (40 8)	23 (37)	7 (24.1)	67 (30.9)
Not examined	12 (33.3)	8 (19 0)	12 (24 5)	17 (27 9)	13 (44.8)	62 (28 6)

(Figures i bracket indicat percent ges)

Table 22. S rvey of the series of non-specified alvula disease.
Males.

	1930—34	1935—39	1940—44	1945—49	1950—54	Total
Number of cases	29	24	22	50	27	152
Group A	5 (17.2)	4 (16.7)	5 (22.7)	10 (20.0)	9 (33.3)	33 (21 7)
Group B	16 (55 2)	9 (37 5)	9 (40.9)	23 (46.0)	14 (51.9)	71 (46.)
Group C	7 (24 1)	9 (37.5)	8 (36 4)	14 (28.0)	4 (14.8)	42 (27 6)
No clinical data	1 (3.4)	2 (8 3)	—	3 (6.0)	—	6 (3.9)
Follow-up 1955						
Deaths	12 (41 4)	7 (29.2)	8 (36 4)	11 (22.0)	7 (25.9)	43 (29 6)
Not traced	5 (17.2)	5 (20.8)	4 (18.2)	6 (12.0)	1 (3.7)	21 (13.8)
Survivors						
Examined	1 (3.4)	7 (29.2)	7 (31.8)	17 (34.0)	2 (7 4)	34 (22.4)
Not examined	11 (37.9)	5 (20 8)	3 (13 6)	16 (32.0)	17 (63.0)	52 (34.2)

(Figures in brackets indicat percentages)

made were thyreotoxicosis and anaemia and pregnancy F r example of 17 females with mitral stenosis and in whom a diag nosis of R.H.D could be excluded 6 had or had had A.R.F at the time of the diagnosis 4 anaemia, 2 thyreotoxicosis, 2 were pregnant and 2 had cardiac neurosis and i 1 th diagnosis had been cancelled on later dmission. Signs f R.H.D can disappear as pointed ut earlier by JACOBSSON (1949) and BLAND & JONES (1952)

Aut psy has also shown that the clinical diagnosis of valvular disease was *sometimes incorrect, but su picion of* valvular lesions was nearly always based n roentgenological or clinical enlargement f the heart owing to cardiosclerosis endocarditis lenta or thyreotoxicosis.

The frequency f excluded cases was highest in th group with mitral lesions (particularly in mitral incompetence) and was of course highest in the group with non-specified lesions, while combined mi tral and aortic and pure aortic lesions were excluded in only a few cases.

per cent, and OLESEN (1955) reported 59 per cent in a conservatively treated series. Chorea minor was seen in 6 (6.8 per cent) of 88.

The mean age at the time of the initial attack of rheumatic fever was 16.9 for those with a firm diagnosis in their history and 20.1 for those in whom the diagnosis had only been suspected. The mean age of the females and that of the males were the same in the group with a firm diagnosis. 16 (38.1 per cent) patients with a firm diagnosis had recurrences of rheumatic fever and 3 of the patients had 3 attacks and 1 had 4. The mean age at the time of the first attack in OLESEN's (1955) series was 15.4, *i.e.* half a year lower than in the operated series and recurrences were somewhat more common — 55 per cent against 38 per cent.

DEGREE OF DISABILITY AT THE TIME OF OPERATION

The degree of disability of the patients at the time of the operation, as judged by the criteria of the N.Y.H.A., is given in the tables below.

It is clear from the figures above that only 4.5 per cent were in group IV against 14 per cent in BADEN's (1958) series. This may be due to differences in selection and/or to the fact that in the present investigation patients belonging to group III to IV were assigned to group III. If the patients in group III to IV had been assigned to group IV, the frequency would have been 9 per cent. Most of the patients (83 per cent) were in group III

Functional class at the time of operation

Functional class	Females	Males	Total
II	8	3	11
	(12.1)	(13.6)	(12.5)
III	55	18	73
	(83.3)	(81.8)	(83.0)
IV	3	1	4
	(4.6)	(4.6)	(4.5)
Total	66	22	88
	(100.0)	(100.0)	(100.0)

(Figures in brackets indicate percentages)

and no difference was found with sex. In the literature the figures for group IV vary between 6.4 per cent (BAILEY 1955) and 40 per cent (COOLEY & DEBAKEY 1954). For group II the values also vary according to range of indications for surgical intervention.

It is evident from the figures below that the percentage of the cases in group IV did not increase with the ages of the patients and that the mean age of the patients in groups II, III and IV at the time of the operation was 38.2, 38.7 and 40.5 years respectively. The corresponding figures for BADEN's (1958) material were 32.0, 37.3 and 43.0.

COMPLICATING VALVULAR DISEASE

Auscultatory signs of aortic involvement in the form of an aortic diastolic murmur were noted in 9 (10.2 per cent) of the patients and one patient had auscultatory and roentgenologic signs of

Working capacity in relation to age at the time of operation

Functional class	< 20	20—29	30—39	40—49	≥50 age in years
II	1	—	5	4	1
III	1	8	28	28	8
IV	—	1	1	1	1
Total	2	9	34	33	10

131 (58.5 per cent) out of ??? pati ts i.e. the frequ ncy of mitral di ease was roughly the same in both group The number of cases with M.S was 223 (18.2 per cent) in the autopsy series and the number of cases with M S M I wa 27 (5.8 per cent) while the clini al series contained 85 (37 1 per cent) M.S and 44 (19.2 per cent) M.S.M I This difference is due to the previously m ntioned differ ences between the diagnosis and th definition of th diagnosis of M S. a sed by pathologists and clinicians.

Mitral lesions occurred in 83.6 per cent in the autopsy series and in 82 per cent in the clinical series. The corresponding figures in the series of C bot (1926) and of Edström & Cedd (1931) w re 8 (and 87 per cent

The sex distribution of th aut psy series was 2.9/1 (females males) while in the clinical series it was 3.7 1 (females males) for M.S., but for the entire series with stenosis with or without incompe tence it was 2.7 1 and 4 4/1 respectively This discrepancy can be explained by the fact that during the year 19.3 the tim available for re-examination of the males was less than that for examination of th females with a consequent preponderance of females as a result.

A pure M.I was rare in both groups (2 per cent) with a slight preponderance for males.

The frequency of pure aortic lesions was also roughly th same in both series, namely 16.4 per cent and 17.5 per cent. Even if the frequency of pure aortic lesions was equal in the two series the distribution of different types of aortic lesions differed. Th autopsy series included only 3.5 per cent of a rtic incompetence as against 11.8 per cent in th clinical series. The diagnosis f pure aorti stenosis was on the other hand, rare in the clinical series but was seen in 12.7 per cent of the autopsy series. The discrepancy cannot be ex plained simply by the different criteria and methods used for diagnosing the lesions post mortem and clinically but it may be ascribed t nder-diagnosis of A.S. in the clinical series The sex distribution of pa tients with aortic lesions was 1 2.5 (fe males males) in the a t psy series and 1 2.1 (females males) in the l nical series for the same reason as that g n for mitral lesions A rtic lesions occurred in the ut psy series in 44 1 per cent and in the clinical series in 41.5 per cent and the corresponding figures in the series of Cy ot (1926) and Edstr m et l (1934) wer 44 per cent and 51 per cent

Th combination f a rtic and mitral lesions occurred in equ l frequency in th aut psy series and in the clinical series 24 per cent and here too aortic tenosis was much more common in th autopsy series than in the clinical series. The figure 24 per cent is in good agreement with that given by White & Jones in 1928.

COMMENTS

Apart from the preponderance of females in the clinical series there was good agree- ment between the autopsy and clinical series, as well as with figures given in th literature The possibility of an under diagnosis of aortic stenosis in the clinical series cannot h wever be excluded. This *possibility is discussed below*

Pure aortic stenosis was found at utopsy in 59 patients, and of these 38 had had a clinical diagnosis of aortic lesions. In 8 (44 4 per cent) of 18 females and 13 (31 7 per cent) of 41 males the diagnosis of A.S. was not made until autopsy

In these 21 cases the clinical diagnosis had been arteriosclerosis or cardioscle- rosis in 12 essential hypertension with cardiac involvement in 4 myocardial infarction in 3 and aortic aneurysm pancreatic cancer and leukemia in 3. One patient was 58 years old, *5 between 60—69 and 15 above 69 years at death.*

5 patients were in such a poor general condition on admission that a thorough examination was not possibl But all

LEFT ATRIUM

The roentgenogram of the left atrium was studied with the patient in the lateral position (SLOCRS & BROMBART 1052) with the oesophagus filled with barium. Since the re-examination in 1053 showed that the roentgenogram of early cases of mitral valve disease was difficult to interpret, this point received special attention (HALL et al. 1061) In 1 case the left atrium appeared to be normal in 7 it showed a slight posterior bulge in 77 the usual bulge and in 3 a fairly marked bulge

LUNG MARKINGS

The lung markings were increased in 52 (59.1 per cent) cases. The right ventricular outflow tract and the hilar markings were not assessed routinely

HEMODYNAMIC FINDINGS

The right side of the heart was catheterised in 76 cases In no instance was the left atrium or ventricle punctured before operation. The method by which the heart was catheterised has been described elsewhere (BJÖRCK et al. 1053) Of the findings made on catheterisation only the pressure in the pulmonary artery and in the P.C.V. will be accounted for here

The mean pulmonary capillary venous pressure in [illegible]0 cases was 18.3 mm Hg with a standard deviation of ±7.4 mm Hg. In 22 cases the resting P.C.V. was normal (at most 15 mm Hg). In functional class II the mean value was 17.5 mm Hg±2.4 mm Hg and in functional class IV it was 18.0 mm Hg±6.8 mm Hg. The difference between the classes was not significant but class IV consisted of only 3 patients. The effect of physical exertion for at least 7 minutes, according to LEE et al. (1952), was studied in 49 cases, and a rise in pressure was noted from a resting mean value of 16.1±5.2 mm Hg to 30.0 mm Hg±0.1 mm Hg. — The high frequency of normal resting P.C.V. values implied a considerable difference from BADEN's material in which a normal P.C.V. pressure was noted in only 5 out of 141 patients.

The mean resting pressure in the pulmonary artery in 74 patients was 31.1 mm Hg±13.7 The pressure on exertion was not routinely measured. No significant difference was found between the different functional classes. The systolic pressure in the pulmonary artery during rest was on the average 53.5±24.2 mm Hg (range 23—123) WOOD (1054) and BADEN (1958) reported 27 and 47 per cent, respectively with a pressure in the pulmonary artery of less than 50 mm Hg the figure in the present material being 58 per cent. On the other hand in the 2 series referred to above the frequency of very high pressures (100—130 mm Hg) of the systolic pressure was 13 and 8 per cent respectively against 0 per cent. There is, thus, reason to assume that in the present series severe hypertension was less marked than in the other two series. This difference might be explained by a difference in the range of indications.

An analysis of the material showed a tendency towards lower pressures during the latter part of the period but the difference was not significant

COMMENTS

This outline of the pre-operative findings in patients operated upon for mitral stenosis was simply to permit a comparison with other series and to provide a background to the discussion of the survival rate and prognosis of mitral stenosis. The material differs from other series mainly regarding the pre-operative functional status of the patients, since it included only a few in functional class II and IV which is also reflected by the values obtained on catheterisation of the heart the values being lower for the pressure in the pulmonary artery and in the P.C.V. than what is usually found in such series. On the other hand the material did not differ from other series in age and sex distribution.

Table 21 The nat ral hi tory f rheumatic heart disease A t psy series.
Females

Mean age t	M S.	M S A S	M S A S A I	M S M I.(M I)	A S	A S A I (A.L)
First attack f rheumatic fever (firm)	17 7 (33.7)	21 9 (1)	17 2 (44 1)	14 7 (50 0)	17 0 (11 1)	20.1 (50 0)
First diagnosis	42.9 (79.5)	43 0 (85.9)	31 8 (93)	37 9 (73 0)	45 3 (44 4)	43 7 (75 0)
First symptom	45 3 (51 9)	43 2 (85 2)	41 2 (92 6)	41 5 (53 0)	58 8 (83.3)	40 0 (50.0)
First attack of right heart failure	52 0 (62 0)	52.6 (74 1)	49 1 (03.0)	53 8 (40 0)	62.6 (72.2)	56 7 (75.0)
Death	55.7	57 4	53 0	52 3	66 9	60 5
Total	166	27	2	70	18	4

T ble 23. The natural history of rheumati heart disease Autopsy series
Males

Mean ge t	M S	M S A S	M S A S A I	M S M I.(M I)	A S.	A.S.A.I.(A L)
First ttack of rheumatic fever (firm)	15.6 (35.0)	16 0 (44 4)	12.0 (40 0)	20.2 (25 0)	18.5 (17 0)	9.8 (38.5)
First diagnosis	37 3 (80 7)	36.4 (77.8)	30 6 (90.0)	41.5 (50 0)	45 8 (51 2)	33.6 (76.9)
First symptom	41 4 (91 7)	40 6 (91 4)	30.3 (100.0)	51 2 (37 5)	53.1 (78.0)	38 8 (76 9)
First ttack of right heart failure	44 0 (73.7)	43 8 (83 3)	42.6 (00.0)	57.2 (37.5)	55.5 (56.1)	42.8 (38.5)
Death	48.8	47 2	44.4	49.8	60 0	46.7
T tal	57	18	10	16	41	13

Figures in first row indicat mean ge   Figures in brackets indicat percentage

Th mean g at the time f first attack in patients with A.S was slightly higher than in patients with M.S. N statistically ignificant difference was found between the mean age at the time of first attack of A.R.F in the clinical and the autopsy series.

Age distribution f the first attack of A R.F in patients with R.H D in the autopsy series

Years	0—9	10—19	20—29	30
Number of cases	30	84	31	17
Per cent	(18.5)	(51.9)	(19 1)	(10.5)

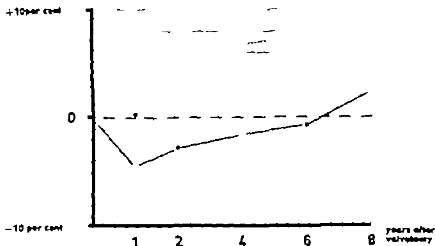


Fig. 31 Mean variation in relative heart volume in terms of per cent of pre-operative alues.
——— pure mitral stenosi at operation (59 cases)
o o mitral incompetence with or without mitral stenosis (22 cases)

tence found at operation (22 patients, including 3 with marked incompetence) an increase was noted in the heart volume. There was, thus a certain agreement within roentgen findings and functional capacity

Of 81 patients, the relative heart volume showed a decrease in 5 within 6 months of the operation. Baden (1958) noted a definite reduction in heart size in 5 per cent as judged by the cardio-thoracic ratio which is surely a less sensitive method. The number of cases with a marked decrease in the relative heart volume was larger in the beginning of the period than during the latter part. This may be due to a wider range of indications and consequently less severe stenosis.

The classification of patients in functional classes cannot, however be more than approximate since it is based upon the patients own opinions of their working capacity and as pointed out by Soloff et al. (19) functional changes in patients with mitral stenosis are cyclical. Moreover differences in occupation naturally limit the valu of su h classification. In addition personal xperience uggest that unlike patients with arterioscleroti or hyperten sive heart disease patients with R.H D are prone to make light of their symptoms. Therefore any classification of patients with M.S., i.e into functional classes may be misleading, if such classification is based entirely or mainly on the opinions of the patients. This phenomenon appears not to have been noticed by workers in this field except by Fahrenkamp (1020) Lichoberg (Personal communication) and Björck (19 0).

Fig. 35 shows that for patients with mitral stenosis at the re-examination in 1953, the prognosis was more favourable in those with sinus rhythm (61 cases) than in those with auricular fibrillation (24 cases) and the classification made by Olesen (19) in which patients with auricular fibrillation and functional class II and III are taken together appears justified.

The relative heart volume is also of prognostic importance (Fig. 36) Of 8. patients with mitral stenosis who had been followed up for at least 5 years after the re-examination in 1953 12 with normal heart volume survived 00 per cent of 32 with a heart volume between 450—699 for females and 500—699 for males, 60

of right heart failure Right h art failure may be insidious but the onset can usually be dated, and often coincides m re or less with degradation f a patient from functional class II t III

Right heart failure appears at an average age of 50 years f r females and f r males and is more comm n I females Th corresponding ages in the clinical series were 49.5 years f r females and 52.1 years f r males and f r patients with M.S 2.0 and 41 0 for females and males respectively Th mean age when right h art failure was ascertained in OLESEN s (1955) series was 4 0 years.

In th clinical series 20 cases with M.S. had had a first attack of right heart failure and none was below 30 years of ag 3 (15 per cent) between 30—39 years (25 per cent) between 40—49 6 (30 per cent) between 50—59 5 (25 per cent) between 60—69 and only 1 (5 per cent) above 69 years at the time of the first attack.

The ag at the time f first attack of right heart failure thus seems to be higher than in the a t psy series and higher than in OLESEN s (1955) series where 33 per cent had had an attack before 40 years of age

AGE AT DEATH

Comparing with the figures given in the literature the mean age at death I the present autopsy material is high and in the clinical series it was 57 8 for females and 55 1 f r males when 51 ut of 220 had died. In pure mitral stenosis in the clinical series the mean age at death was 58.2 and 0 0 years for females and males respectiv ly

The findings I mitral stenosi made in the present material agreed with those of OLESEN (1955) regarding age at the first attack of A R F and at first attack of right heart failure while the ag at first symptoms and the age at death were higher in the present m terial but showed the same tendency as OLESEN s regarding urvival after A.R.F in diff rent ge groups, after ne or more attacks of A.R.F and survival after heart symptoms in different ag groups, etc. Thus, good agreement was found between these tw series.

Ag at right heart failure in the autopsy series

Mitral stenosis

Age	<30	30—39	40—49	50—59	60—69	≥ 0	Total
Number f patients	12	16	4	31	18	13	139
Per cent	8.6	11.5	35 3	22.3	13.0	9 4	100 1

Age t right heart failure in the autopsy series

Aortic stenosis

Age	40	40—49	50—59	60—69	≥ 0	Total
Number f patients	3	4	7	7	2	23
Per cent	13.0	17 4	30.5	30.5	8.7	100.1

per cent of 15 with a heart volume between 700—1 000 and 17 per cent of 6 patients with a relative heart volume of more than 1 000 cc/m body surface survived.

The difference between the groups regarding relative heart size may in some measure, be due to differences in age but in the two groups with the largest relative heart size the mean age at the re-examination was one and the same (54.5 and 54.3 years). In a further investigation in progress, this is receiving detailed attention.

RE STENOSIS

5 patients were operated upon for re-stenosis out of 81 and some others are on the waiting list. Is re-stenosis due to rheumatic activity or inadequate valvotomy or healing of the ruptures made by the operator? Some authors (BAKER 1960) claim that the valvotomy was not always sufficient in the beginning of the 50ies, but at the same time state that systolic murmurs disappear which should suggest re-stenosis. None of the patients re-operated upon had any clinical manifestation of A.R.F and biopsy of the left auricle showed Aschoff granulomas in only one case (see also BJÖRCK et al. 1952), and only in one case was the AST more than 300 U at operation. Repeated controls after first operation showed normal E.S.R.s. The material is however too small to permit any valid conclusions and until it is known whether rheumatic activity exists in the high age classes, or not the prophylactic use of penicillin may be regarded as indicated. If rheumatic activity is suspected penicillin therapy may be advisable (MORTIMER et al. 1959 SZEKELY 1950).

Mean age at death in patients with rheumatic heart disease

Total material

Period	1930—34	1935—39	1940—44	1945—49	1950—54
Females	4[illegible]1	52.0	54.2	56.1	58.0
Males	40 0	4[illegible]	47.2	[illegible]0 0	50 1

HAS THE PROGNOSIS IMPROVED DURING THE PERIOD COVERED BY THE PRESENT INVESTIGATION?

MÜLLER (1956) in Oslo found that the prognosis of aortic and mitral stenosis has improved during the last decades. One might imagine that the improvement in the prognosis for the population as a whole also holds for patients with R.H.D and since our therapeutic arsenal has undergone considerabl improvement during this period, the prognosis of R.H D should reasonably also be better fo the youngest group than it was for the oldest The mean age at th time f death f patients in the group with a firm diagnosis of R.H.D., irrespective whether the patient died in hospital or at home is given above

There was thus a clear tend ncy for the mean duration of life to increase for patients with R H.D and a difference between the 30ies and the 50ies in this respect was almost significant ($P < 0.05$) for females and significant ($P < 0.01$) for males calculated according to WILCOXON (1945). It is obvious that the prognosis for the males was gloomier than for females in the beginning of the period of the investigation.

Is any difference demonstrable between the groups with rheumati valvular lesions who died at hospital and those who died at home? Th mean ages of those with a firm diagnosis of R.H.D who had died in th hospital (autopsied, not autopsied) or had died outside the hospital are given in th table below

There is no reason to suppose that the prognosis as judged by evaluation of the autopsied patients with valvular lesions was in any way biased but they seemed t be representative of the entire group of patients with valvular disease who satisfied the criteria set up by N Y H.A.

Mean age at death

		Females	Males
Died in hospital	Autopsied	55.1	50 4
	Not autopsied	[illegible]1 4	48.2
Died outside hospital		53.8	50.9

The improvement of the prognosis of R.H.D also applies to males with M.S. in the autopsy series in which the mean age at death was 41.8 years during 1930—39 46.3 years during 1940—49 and [illegible]6 1 years during 1950—58 while for females the corresponding figures were 54.2 54.7 and 58.5 years. According to WILCOXON (1945) the improvement of the prognosis in 1930—39 to 1940—49 was almost significant ($P < 0.05$), and the result obtained in 1940—49 to 1950—59 was also almost significant. The difference between 1930—39 nd 1950—59 was significant ($P < 0.01$) while the difference in the females was not. In the clinical series the mean age at death was 59 0 for females and 58.2 for males with M.S., when 27.8 and 17 9 per cent had died.

If the autopsy series (excluding pure aortic stenosis) be divided into one group with A.R.F in the history and one without, it will be seen that the prognosis is possibly slightly better in the former group but statistically significantly ($P < 0.001$) better in the latter group

Table 26. *The natural history in mitral stenosis*

Mean age at	Autopsy series F	Autopsy series M	Clinical series F	Clinical series M	Operated series F	Operated series M
Acute rheumatic fever (firm)	17.7 (33.7)	15.6 (35.0)	16.0 (56.7)	21.1 (55.6)	16.7 (45.5)	16.9 (50.0)
Acute rheumatic fever (probable)	25.4 (16.9)	16.2 (14.0)	21.8 (9.0)	26.5 (11.1)	20.4 (18.2)	19.8 (27.3)
First symptom	45.3 (81.9)	41.4 (94.7)	40.0 (82.1)	42.4 (61.1)	31.1 (100.0)	32.8 (100.0)
First attack of right heart failure	52.0 (62.0)	44.0 (73.7)	48.4 (25.4)	50.8 (27.8)	37.6 (42.4)	37.1 (36.4)
Death	55.7 (100.0)	48.8 (100.0)	53.2 (17.9)	50.0 (27.8)	45.5 (16.7)	43.3 (31.8)
Total	166	5	67	18	66	22

Figures in first row indicate mean age. Figures in brackets indicate percentages.

years for females and 41.3 years for males. It should be observed that 18.1 per cent of the females and 5.3 per cent of the males had no symptoms at all. If the first symptoms are to be understood as limited or impaired working capacity. The mean age at the time of the first symptoms in the clinical series did not differ appreciably from that in the autopsied series and it was 40.0 years for the females and 42.4 years for the males. OLESEN (1955) reported a mean age of 30.5 years and 32.5 years, respectively for the first symptoms which is thus at least 10 years lower than that in the autopsy and clinical series of the present material. The operated group on the other hand showed a low mean age at the time of the first symptoms, namely 31.1 and 32.8 years. The first symptoms are not to be understood as an attack of embolism of bacterial endocarditis. It is true that a symptom of decreased working capacity may persist immediately from the first attack of A.R.F but as a rule the patients are symptom free during a relatively long period after which symptoms develop e.g. in association with complicating diseases or pregnancy.

RIGHT HEART FAILURE

The mean age at the time of the first attack of right heart failure in the autopsy series was 51.3 years for the females and 44.0 years for the males and signs of right heart failure occurred in 62.7 per cent of the females and in 73.7 per cent of the males. The corresponding figures for the re-examined group were 48.4 years for the females and 50.8 years for the males while in this group only about 25 per cent reached the stage of a first attack of right heart failure. The operated series, on the other hand, showed a much lower mean age for right heart failure namely 37.6 years for the females and 37.1 years for the males, and the figures are based on 42.4 and 36.4 per cent of the material, respectively. The mean age at the time of the first attack of right heart failure in OLESEN's material was 45.6 years which is a few years lower than that for the autopsied and re-examined

OPERATED SERIES

Between 1950 and 1958 a total of 88 patients were operated upon for mitral stenosis (Professor H. Wulff Docent A. Malm). Of thes 44 were resident f Malmö and 44 came from other places in the south of Sweden. The frequency of operation for mitral stenosis in Malmö was 1951 — 7 19 2 — 12, 1953 — 10 19 1 — 6, 1955 — 2, 1956 — 3 and 1957 — 4 This corresponds to 0.35 per 10,000 inhabitants per year during 1950— 1 and implies that 1/3—1/4 f patients with mitral st nosis are operated upon. The indications used throughout the above-mentioned period were those originally defined by the f rmer director of the heart laboratory Biörck et al. (1953 and 1955) and data from th operated series have been published elsewhere (*Biörck et al. 1952, Biörck et al.* 1953, Werkö et al. 1953 Wulff et al. 1953, Bülow et al. 1955 Overbeck et al. 1955 Biörck et 1. 1955).

AGE AND SEX DISTRIBUTION

Th series consisted f 66 f males and 22 males. The sex distribution was largely the same as that in B den s (1958) series (72 per cent and 28 per cent, respectively) and that in most other series, in which 70—80 per cent consisted of females (January t al. 1957 Turner 1957 Ellis et al. 1950).

The youngest patient was 9 years and the ldest 57 and the averag age at th time f operation was 38.7 years which is very close t that in Bailey's (1955) and Ellis t al.s (1959) series, in both f which it was 30 years. In the present series *the mean g did not differ significantly* with sex and was 39 1 for the females and 37.8 for the males.

Age and sex distribution at the time of operation

Age	Females	Males	Total
<20	—	2	2
		(9 1)	(2.3)
20—29	7	2	9
	(10.6)	(9 1)	(10.2)
30—39	26	8	34
	(39 4)	(36.4)	(38.6)
40—49	26	7	33
	(39 4)	(31.8)	(37.5)
≥50	7	3	10
	(10 6)	*(13.6)*	*(11 4)*
Total	66	22	88
	(100 0)	(100.0)	(100 0)

(Figures in brackets indicate percentages)

The ag distribution was approximately the same as in ther operative series. In Ellis & Harken's (1955) series for example 37 per cent were 30—39 years and 38 *per cent were 40—49 years.* The percentages in these classes were somewhat higher than in Baden s (1958) material where 21 per cent of the patients were below 30 years, as against 12.5 per cent in the present material and the figures f r patients above 50 years were 5 per cent and 11 4 per cent, respectively

ACUTE RHEUMATIC FEVER

Of the 66 women who had been operated upon, 43 (65.2 per cent) had rheumatic fever in their history and in 31 (47 0 per cent) the diagnosis was regarded as firm. The corresponding values for the 22 operated males were 17 (77.3 per cent) and 11 (50.0 per cent). Baden (1958) gave a somewhat lower frequency namely 55

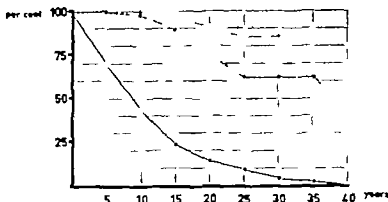


Fig. 39 *Mitral stenosis.*
S rvival after onset f first heart symptoms.
Females.

——— autopsy series (13. cases)
o clinical series (55 cases)
+ + operated series (61 cases)

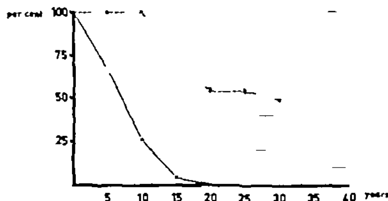


Fig. 40. *Mitral stenosis.*
Survival after onset of first heart symptoms.
Males.

——— utopsy series (54 cases)
clinical series (12 cases)
+ - operated series (20 cases)
(Series not strictly comparable)

figures were 16.7 per cent and 31 8 per cent respectively and the mean age 45.6 and 13.3 years, respectively

It may be claimed on the basis of the above-mentioned figures that there is no appreciable difference between the autopsy series and the clinical series regarding age at the time of the first attack of A R F., the frequency of A.R.F in the history age at time of first symptoms or age at time of first attack of right heart failure but there was one difference which was that in the clinical series only 2. per cent reached the age of right heart failure and that the

involvement of the tricuspid valves None of the patients showed signs of aortic stenosis but in 5 of the patients with an aortic diastolic murmur there was also a basal systolic murmur The frequency of complicating valvular disease in mitral stenosis varies from one surgical series to another (Logan & Turner 1953 Baden 1958).

ELECTROCARDIOGRAPHIC ABNORMALITIES

Auricular fibrillation was noted before operation in 3 (4 per cent) which is in good agreement with Baden's (1958) figures and somewhat lower than the values reported by Bailey (1955) The abnormality was found in 25 (37.9 per cent) of 66 females and in 12 (18.1 per cent) of 22 males a distribution consistent with those described by Olesen (1955) and Baden (1958). In class II the frequency of auricular fibrillation was 25 per cent for the females and 33.3 per cent for the males while in class III it was 41.8 and 55.6 per cent respectively In the small class IV only 1 patient had auricular fibrillation, while the others had sinus rythm.

The electric axis was normal in 40 (60.6 per cent) of the females and in 16 (72. per cent) of the males. There was right axis deviation in 21 (31.8 per cent) of the females and in 6 (27.3 per cent) of the males. Left axis deviation was seen in 5 (7.6 per cent) of the females. Right ventricular hypertrophy was observed with certainty in 16 (24.2 per cent) of the females and 4 (18.1 per cent) of the males. In 8 other females the electrocardiographic recordings were inconclusive In 3 patients there were signs of left ventricular hypertrophy in whom operation showed signs of mitral incompetence in 2 and isolated mitral stenosis in 1 in whom commissurotomy was followed by signs of associated aortic disease

ROENTGEN FINDINGS

The relative volume of the heart is given in the table below where the patients are also grouped according to working capacity and age The relative heart volume was determined by the method of Liljestrand Lysholm Nylin & Zachrisson (1939) and the normal values for the relative heart value as judged by this method, are at most 450 for females and 500 for males.

It is clear from the table that the relative volume of the heart before operation was normal in 5 (5.7 per cent) slightly enlarged in 63 (71.6 per cent) markedly enlarged in 17 (19.3 per cent) and extremely enlarged in 3 (3.4 per cent). No comparison was made between the relative heart volume and the cardio-thoracic ratio

It should be observed that in Baden's (1958) series of 166 patients 88 had a cardio-thoracic ratio of less than 55 which was regarded as a group which chiefly comprise hearts of normal size Similar results have been published by Logan & Turner (1953) and Baker et al. (1952) who found 49 per cent and 48 per cent, respectively to have a cardio-thoracic ratio of less than 55.

Pre-operative relative heart volume

Functional class	F <450	M <500	F 450—699	M 500—699	F 700—999	M 700—999	F ≥1,000	M ≥1,000	Total F	Total M
II	—	1	8	2	—	—	—	—	8	3
III	4	—	40	10	9	7	2	1	55	18
IV	—	—	3	—	—	1	—	—	3	1
Total	4	1	51	12	9	8	2	1	66	22

1960)) th prognosi in surgically treated patients is better than in those treated conservatively but Laas et al (19 3) tress the difficulty in obtaining accept able controls. The ideal method to compare surgically treated patients with patients treated conservatively would be o operate upon every other patient w th M.S., but such a procedure is not pos ible

The survival rates *from* the first attack f A.R.F from the first sympt ms and from he first attack of right heart failure are gi en schematicall below for the aut psy clinical and operated series. As expected the lowest survi al rate was found f r the autopsy series from 1930—58.

The survi al rate (Figs. 37 and 38) from th first attack of A.R.F was larg ly the same in the clinical and the perated series. In the autopsy series however the survi al rate was lower In all three series the prognosis was worse for males.

The mean age at the time of th first symptoms in *the* operated series wa about 32 ears, and about 40 in the other tw According to OLESEN (195) younger patients have better prospects of longer survi al and similar results were found in the present in estigation. In the aut psy series the survival after 10 years wa 61 per cent for both sexes with first sympt m at the age between 30 and 49 and onl 20 per cent at ages abo e 50 Th urvival rat (Figs. 39 and 40) from the first mptoms was largel the same in th linical and th operated series.

In th aut ps series more than 60 per cent had died within 1 ear f th nset f right heart failure (Figs. 41 and 42) whil n the clinical series it wa les than 2 per cent with n ears and o er 50 per cent after 8 10 ears. These figures are m re f ourable than those gi en b OLE EN (195) who reported 12 per cent urvi al aft r 3 ears Th d screpancy ma be xpla ned b th hang n urv al after the onset of right heart failure during the last decade See p. 96. In the autopsy series during 1930—39 and 1940—49 the survival after 2 years was 25 per cent as against 55 per cent during 1950—59 for patients below 50 years at the time of onset of right heart failure The same tendency was n ted for patients above this age The survival after 2 years in 1930—39 was 10 per cent 1940—49 25 per cent and 1950—59 37 per cent This might be due to perati n and/or better therapeutics.

The coincidence of the improvement with the advent of heart surgery is remark able th ugh the possibility of factors other than surgery cannot be excluded with certainty The improvement in the surgical series from the first attack of right heart failure can hardly be ascribed to any *differences* in age distribution between the clinical and urgical series, since the autopsy series showed the same sur ival rate after 2 years independently of age at the time of the *first* attack.

Summarizing, though the 3 series are not strictly comparable it would appear that surgical treatment improves the life expectancy of patients *with mitral* stenosi In view of recent ad ances in heart surgery th operative mortality and the beneficial effect n the well-being of the patient it would appear desirable to examine all patients with M.S. regarding the advisa bility f *offering* surgical treatment. This is all the more important because valvoto- m is generally accepted as a prophylactic measure against arterial embolism and in th autops series 15.8 per cent of the patients with M.S. showed signs or sequele of cerebral emboli. Un-operated and operated patients with M.S. from the period 1950 60 have been re-examined with respect t this probl m, and the results will be published elsewhere (HALL et al. in pres).

RESULTS OF OPERATION

		Functional class at the re-examination in 19 9				Operatls deaths	Late deaths
		I	II	III	IV		
	II	4	4	2		1	
Functional class at the time of operation	III	10	28	1J	1	6	9
	IV			1	1		2

During 19J0– 57 88 patients were perated upon for mitral stenosis. The operation claimed earl post-operat v deaths and late deaths occurred in 11. Moderate incompetence was found in 10 patients, and severe in 3 at th peration. The primary operative mort lity wa 8 per cent (" cases) and th deaths in rela tion to number f operations during th 19J0—33 period were 12.5 per cent the corresponding figures f th 19J4 5 period and 19J6—J" wer 6 and 0 per cent respectively. A similar decrease in operative mortal ty has also been described by SOULIÉ et al. (19J3) nd B KER (1960).

Of the surviving 0 patients 69 were reviewed (1 unabl to spare time for examination in 19 9).

The survey above shows that to 9 years after operation, 42 were graded up at least one functional class, that 21 wer in the same class, that 4 had been degraded and that 11 had died. BAKER (1960) rep rted 28 deaths of 200 within 6 years g bo ut th same late mortality. The fre quency f improvement after operation is in good greement with figures in the literat u (ELLIS et al. 19 9, B KER 196)

Th results in th first 23 perated patient re given below

In this group of patients there were 21 n functional class III and 2 in functi nal lass II befor operation, and the figures suggest improvement during the first 6 years after operation, after which th bene ficial effect of the operation is less marked. This is lso reflected by th relative heart volume (Fig. 34). The figure shows the mean variation in the relative heart volume in terms of per cent of pre-operative values. In the first 49 patients operated upon for pure M.S. the siz was less than that before operation for 6 years and then increased. In th patients with incompe

Years after operation	Functional class				Operative deaths	Late deaths
	I	II	III	IV		
2 years	3	10	5	—	4	1
4 years	2	11	4	—	—	1
6 years	2	11	4	—	—	—
8 years	1	7	8	1	—	—

two last 5-year periods. However analysis of the number of admissions, the frequency of right heart failure and mortality per 5-year periods, suggested no change in the range of indications for admission. During the last 5-year period however there might have been a slight increase in the number of admissions of less severe cases (observation for operability).

Analysis of the standardised morbidity rate of R.H.D. showed largely an and the same rate during 1930—50 and then a decrease and secondly the decrease was due mainly to a decrease in the frequency of the disease in the l w age groups (Tables 12 and 13) and thirdly a shift t wards higher ages f r males, but not for females. This gives rise to the question whether the prognosis might have improved during the investigation period.

The number of patients still alive on January 1 1958, was ascertained from a search of the parish registers. About 10 per cent of the entire material, mainly from the years before 1910 could not be traced. The mortality during the observation period from 3—28 years was 50 per cent for the group with pure mitral lesions, 60 per cent for those with combined mitral and aortic lesions and 70 per cent for those with pure aortic lesions. Thus, a total of 8.2 patients had died, and of those 163 or 51.3 per cent had shown evidence of R.H.D. at autopsy.

On review of patients with a clinical diagnosis of R.H.D. during 1930 . . . it was f und that the diagnosis could be excluded in about 30 per cent. It was mainly in patients with a diagnosis of mitral lesions, particularly mitral incompetence that the diagnosis was excluded. This pre-ious . . ver-diagnosis might have been due to such conditions as acute rheumati f ver anaemia thyreotoxicosis and pregnancy.

In . ther cases th diagnosi coul n t be . xcluded with certainty because of s . pected auscultat ry roentgenological r . lectrocardiographical findings. On furth . pecial i . estigat . of th group which was originally 10—20 per cent of the re-examined patients, it was found that in about half of them the grounds for suspecting R.H.D. were very meagre.

A probable r suspected diagnosis had been made in a fair number of *young* patients during the investigation period. Increa ed resources and refinement of dia gnostic methods will probably reduce the number of uncertain diagnoses in the future.

The re-examination showed a total number of 229 patients with valvular lesions (clinical series). The above-mentioned autopsy series — 463 patients — gives a panorama of the entire investigation period and probably gives the gloom iest prognosis of R.H.D. while the clinical series gives a representative snapsh t of the surviving patients. Comparison between the autopsy and clinical series showed fairly good agreement regarding the relative frequency of different diagnoses, with the exception of clinical under diagnosis of A.S.

The natural hi tory of R.H.D. is discussed and elucidated from the following milestones, mean age at the first attack f A.R.F., mean age at the first symptoms mean age at the first attack of right heart failure and mean age at death. No difference was f und between the mean age at the time of the first attack of A.R.F. and the mean age at the time of the first heart sympt ms in the autopsy and in the clinical series (11.3 and 42.8 years, respectively).

This is remarkable and suggests n correlation between the severity of A.R.F. and th durati n of survival from first attack to first heart symptoms. The autopsy series dates back further than the clinical series.

Right heart failure appeared at a high mean ag in the aut psy series (Tables 21 and 25). In the clinical series a few patients had had right heart failure and the mean ag of the last mentioned patients was till higher. This might suggest an improvement of the prognosis during the latter part of the investigation.

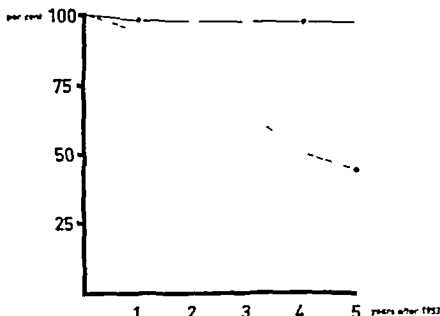


Fig. 35. Survi al f patient with mitral stenosis ith sinus rh thm —— and auricular fibrillation t re-examination in 1953.

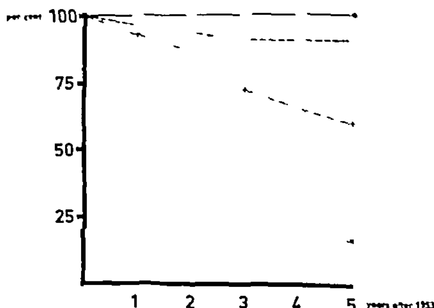


Fig. 36. Survival of patients with mitral stenosis grouped according t relative heart volume t re-examination in 1953.

—— < 450 and < 500
○ 450—699 500—699 for females and males, respectively
+ - - + 700—1,000
+ + ≧1,000 cc/m² body surface

investig tion are briefly outlined against the background of publications by earlier workers in this field.

Good agreement with the report f pre rious investigations was f und in the f ll ing respects.

The distribution of valvular lesi ns (pure mitral 5 per cent mitral and aortic 21 per cent and pure a rtic 17 per cent)

The sex distribution of mitral stenosis (females males — 3/1) and aortic stenosi (females males — 1/7).

The frequency of acute rheumatic f ver in the history of patients with rheumatic heart disease (50—60 per cent except in patients with aortic stenosis — 10—20 per cent) without any change in frequency during the investigation period

Acute rheumatic fever appeared at mean age of about 18 years.

The mortality within 3—28 years after first admi sion among patients with a diagnosis of pure mitral lesions was high (50 per cent) but higher among those with combined mitral and aortic lesions (60 per cent) and highest among those with pure aortic lesions (0 per cent)

The prognosis in pati nts with aortic stenosis which showed no change during the investigation period (mean age at the first attack of acute rheumatic fever 18 at the first heart s mptoms 55 at the first attack of right heart failure 58, and at death 62 years. At the three last menti n ed milestones the mean ages of the females were about 6 years higher than those f the males).

Th pre-operative find ngs in the opera ted series f mitral stenosis.

Surgical treatment in mitral stenosi is uperior to conservativ treatment.

The f ndings in the present material dif fered n the follow ng respect from what i widely bel eved n thi field

Th freq ency f rheum tic heart dis ase sh wed no decrease bef re 19 0

Th low incidence f m tral incompe tence (per cent in th t ps nd th l ni l series)

Mean age in patients with rheumatic heart disease in the autopsy series at the time of the first heart symptoms (about 43 years) at the time of the first attack of right heart failure (about 47 years) and at death (about 51 years). At the three last mentione l milestones th mean ages of the females were higher than those of the males.

Mean ag in patients with predominant mitral tenosis in the autopsy series at the time of the first heart symptoms (about 13 years) at the time of the first attack of right heart failure (about 50 years) and at leath (about 1 years). At the three last mentioned milestones the mean ages of the females were higher than those of th males.

No significa t difference was found be tween th ages at the time of the first symp-toms in the clinical and the autopsy series.

Mean ag at the time of the first heart ymptom in patients with mitral stenosis was 11 years in the aut psy series, and 40 years in th clinical series.

Mean age at the time of the first attack f right heart failure was in patients with mitral stenosis 50 years in the autopsy series, and 43 years in the clinical series.

Mean age at death in patients with mit ral stenosi wa 51 years in the autopsy series and 59 years in the clinical series.

The survival after the first attack of right heart failure has improved especially in patients with mitral stenosis, during the investigation period and most markedly after 1950

The over all prognosis of rheumatic heart disease has probably improved (but not f r patient with aortic stenosis). The improvement was statistically signifi cant only for patients without acute rheu matic fever in the history A similar ten dency wa noted for patients with mitral tenosis

In the maj rity of the operated pati nts with mitral tenosis th beneficial effect of operation as judged by functional capacity and relativ heart v lume lasted 6—8 years fter which it graduall diminished.

THE PROGNOSIS OF MITRAL STENOSIS

The concept of the natural hi t ry of mitral stenosis has varied from n period t another as is apparent from a urvey of the literature and pinions based n clinical series will leave a somewhat different impres ion than that based n autopsy material. In this chapter the prognosis will be elucidated on the ba is f both types of mat rial An aut psy series (total 223 cases) from th years 1930 58 and a cl nical series (85 patient) r examined in 1953 and admitted t th hospital during the years 1930 50 In addition the course in 88 patients perated upon in 1950 58 for mitral stenosis will also be dwelt n. There is a certain overlapping of th three series n that th clinical series in luded 31 pati nts wh had died befor January 1 1958 and 26 had been utopsied and are included also in the aut psy series, nd 13 pat nt belonging to clinical series were perated upon for mitral tenosis bef re th beginning of 1958 6 patients belonging t the operated series were also examined post-mortem. This o erlapping must be born in mind n the evaluation of any conclusion that may be drawn from the various series.

The survival rat is calcul ted from the various milest nes. Acute rheumatic fever first symptoms and first attack of right heart failure

ACUTE RHEUMATIC FEVER

T ble 26 shows th mean age at the time of th first attack f rheumatic fever at th time of th first symptoms and of death in the autopsy clinical and operated series.

The frequency of A.R F in patients with mitral tenosis showed that 50 to 75 per cent in th different groups had a firm or probable diagno is of rheumatic fever in thei history but the autopsy group showed a somewhat lower frequency f A R F than the other two groups.

Th number of cases with probable A.R F w s smallest in the group examined which is surely due to th more detailed history in that group The mean age at the t m of th first attack varied somewhat between 1 6 and 21 1 years for patients w th a firm diagnosis of A.R.F while the mean ag f those with a probable diagnosis wa throughout higher Chorea minor occurred in the aut p y series in 6 per cent f the females and in 7 per cent of the males while the xamined group sh wed 20 9 and 11 1 per cent respectively

No significant difference was found between the different series regarding the age at th time of the first attack of A.R.F

The number of recurrences f A.R.F among the autopsied females was 21 r 23. per cent and among the males 10 or 17.5 per cent In the clinical series the corresponding figures were 24 (29.2 per cent) and 3 (21 4 per cent) respectively while the operated series had recurrences in 13 (44 8 per cent) and 3 (27.3 per cent) respectively The higher frequency of recurrences in the latter group may probably help to explain why these patients with mitral stenosis had the worse prognosis.

AGE AT ONSET OF HEART SYMPTOMS

The mean age at the time of the first symptoms in the autopsy series was 45.3

Byw ters, I C L. & T omas, C T., Treatment and prevention of rheumatic fever in. Modern trend in cardiology Edited by A. M. Jones B tterworth & Co Lo don 1960 p 100.

Caro R. C., Trans. A Amer Phycns 21.22, 1914.
— Fact on the heart. W B. Saunders Co. Philadelphia, 1926
C m btle, M & Sn cale J W Brit. med. J 1.328 1932.
Ca lls D L., J Mich med. Soc. 57.53 1958.
C t zaro F J Stetso C. A M nis, A. J Cram itz, R Rammelkam C. H. J Stolzer, B L. & Perry W D Amer J Med 17 49 1954
Ch No, H. T & Lir C. C., Chin. med. J 6.323 1938
Claibor e, T S & Wolff R. P Sth. med. J 31 681 1941
Clawso B. J Amer Heart J 22:607 1041
Clawson B. J N ble, J F & Luther N H Amer Heart J 15.58 1935
Clel d J B., Med. J Aust. 2:352, 1931
Clemmensen S., Acta med scand., Suppl. 221 1949 p. 100
Cobb, S., Mynch t W R. & W bar J Ch J hron Dis 2:50 1954
Co ter, A F J Amer med. A s. 126.88, 1944
Contr tto, A. W & Levi e, S A., Ann. intern. Med. 10:1836 1937
Cooley D A & DeB k y M. E., J Amer med. Ass. 155:235, 1954

Debré, R., Mozzicon cci P & N lle, J Arch Mal. Coeur 48 6 1955
D chend G M J & Hr m N G R. Tex. St J Med 39:229 1943.
D (A. C. & Lindo C. Amer Heart J 1 478 1935.
D (A. C. Li oo C. & Com A. E., Amer Heart J 10:4.9 193.
Di ll, L. J & Ram n, A. C. Amer J Dis Child 61 1014 1941
Di l W W w ker, L. W & Rammel (H Amer J Dis. Child. 40:506, 1
Do A K. Ll B S. Ar n, L. E., Seely J B & K lle l C Pediatrics 15:.22, 1 5
I R J J Bull. Sch. Med. Maryland 43 1 5
I u I H w d Balls c, R S m ll, I & D I Sem Hôp Paris 31:2333, 19

Ere (Febri heumatica AB Gleerups, Lund, 1935
Ester w (& (( ) Act med scand. 117:377 19 (
La sch, H Scand J b l b l est Suppl 4 1 5

Ellis, L. B. & Harken D. L., Circulation 11:637 1955.
Ellis, L B., H ken D E. & Black, H. Circulation 19:803, 1959
F y J L. & Ellison th R. S., Arch. Dis. Childh. 26.304 1951

F ken M. K., Nervenarzt 2:697 1920
Fei stei A. R. & Di M asa R., New Engl. J Med. 260:1001 1959
Flemming, D S., Hirschbo ck I J & Gonorrf J A., Minn. Med. 30.208 1956.
F edberg C. K., Circulation 19:161 1959

G sp A. & Ogoer k J Z. Rheumaforsch. 1 .33, 1938.
G ll, T J Geront. 6.327 1951
Gelfm R., Ann. intern. Med. 19.253, 1943.
Gibbs, A. J Guy' Hosp Rep. 85:275, 1935.
Glover, J A. Lancet 2:51 1943.
Godtfredsen E., Acta ophthal. 32:717 1954
Goldm n M J Principles of clinical electrocardiography Lange Medical Publications, Los Altos, Calif. 1956.
Gram m, S., Brit. med. J 2:721 1955.
Gr nt R. T Heart 6.275, 1933.
Gr sen P Die rheumatisch Erkrankung bei Kindern in. Die Prognose chronischer Er krankungen. Herausgegeben on F Linne w h. Springer Verlag, Berlin 1960 p. 375
Gross, L. & Kugel, M A., Amer J Path. 7 445 1931
Gutzeit H & Wan urg, L., Act med. scand., S ppl. 249 1951 p. 90

H ll, P & B ober, C Acta rheum. scand. 4 70 1938.
H ll, P Ihö ck G & Olsso N M Acta med scand. 160 313, 1961
H ll, P Denck n, S J & B eck, C Amer Heart J 41 600 1952.
H nsen A. E., J Pediat 23:296 1940
H ssen P T norsk Laegeforen. 77 143, 1957
Har en D E., Black, H. T ylo W J Thrower, W B Soroff H S. & Bush, A Amer J Cardiol. 4 135 19 9
H rso T R. & Levi e S A., Sth. med. J 1 :014 1924.
Har ing, I Nord. Med. 31.2127 1946
He na th J Cited by Hedley O F 1940.
Hedley O F Publ. Hlth Rep. 54.2271 1039.
— Publ. Hlth Rep 55:1647 1940
— Publ. Hlth Rep. 55 1707 1940.
Hirschfelder, A. D Disease of the heart nd aorta. 3. ed. revised. J B Lippincott Co Philadelphia, 1918.
Hitch s, R. A. N A n. rheum. Dis. 15:160 1956
H ll on W P J Amer med Ass. 176 81 1944
H H N Arch Path (691 1949

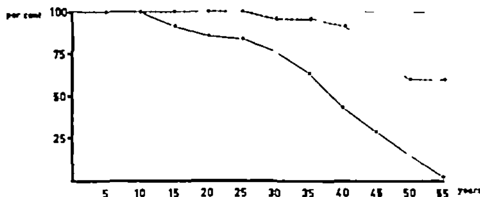


Fig. 37 *Mitral stenosis.*
Survival after onset of acut heumatic fever
Females.

——— utopsy series (75 cases)
o o linical series (35 cases)
+ + operated series (30 cases)



Fig. 38. *Mitral stenosis.*
Survival after onset of acut rheumatic fever
Males.

——— autopsy series (19 cases)
o clinical series (11 cases)
+ + operated series (9 cases)
(Series not trictly comparable)

series in the present material where the corresponding figures were 49 7 and 49.0 years respectively

AGE AT DEATH

The mean age at the time of death in the autopsy series was 55.7 years for the females and 48.8 years for the males, *i.e* a higher mean age than that given by OLESEN (1955), who gave 47.3 and 46 1 years respectively In the clinical series 17.9 per cent of the females and 27.8 per cent of the males died at a mean age of 58.2 years and 59 years, respectively and in the operated series the corresponding

Rheumatism and Arthritis. Review of American and English literature of recent years. Ann. intern. Med. 39:498, 1953.
Rheumatism and Arthritis. Review of American and English literature of recent years. Ann. intern. Med. 50:366, 1959.
Rogers, H. Cited by Jacobsson, E., 1946.
Rogers, L. S. Arch. Otolaryng. 67:569 1958.
Roper, M W., Bennett G A., Cobb, S., J cox, R. & Jessar, R. A. Ann. rheum. Dis. 16:116 1957
Roth, L R., Lingg, C. & Whittemore, A. Amer Heart J 13:36, 1937

Saslaw M. S., Hernandez, F A. & Randolph, H E. Amer J Cardiol. 3:754 1959
Saslaw M. S., Hernandez, F A. & Wenslow S. C. J Pediat. 44:414 1954
Sch ödt T. Acta Med. leg. soc. 9 247 1956.
Segal, J Hartley W P & Hutn gel, C. Amer J Med. 21:290, 1956.
Seghers, M. & Bronkart M. Acta cardiol., Suppl. 5, 1952.
Selander, P Personal communications.
Snedecor, G W Statistical methods applied t experiment in agriculture and biology 4 ed., Ames, Iowa, Iowa State Collegiat Press, 1946.
Soloff L. A. & Zatuchn J Amer J Med. 18:419 1953.
Soulié, P Di Matteo, J & Ahmad J Bull. Soc méd. Hôp. Paris 71 742, 1955.
Stollerman G H Amer J Med. 17 57 1954
S ollerman, G H Glick, S Patel, D J Hirschfeld I & Rusoff J H. Amer J Med. 15 645, 1953.
Sydenham T Cited by Wilson, M G., 1940.
Szekely P Newc. med. J 26:33, 1959

T L M. J Pediat. 29·77 1946.
T a, A. & Stollerman, G. H Amer J Med 20:170 1956.
Thomas, A E Ann. rheum. Dis. 14:259 1955.
Th li K L Nord Med. 52:1262, 1954.
Treatment of acut rheumatic fever in children. Co-operati clinical trial of ACTH, cortisone and aspirin. Brit. med J 1:555, 1955
T alo L H Ann rheum. Dis. 19 174 1960
T an B W Acta cardiol 12:475, 1957

U S N tional Office of Vital Statistics. V tal St tistics Spec Rep N t Summaries 44 N 1 1956

Waaler, E. Acta med. scand. 160:293, 1958.
— Acta med. scand. 160:281 1958.
Wallace, H M. & Rich H Amer J Dis. Child. 89·7 1955.
Wallg en, A. Ann Paediat Fenn. 3:516, 1957
Wannam ker, L. W Rammelkamp C. H. Jr, Denny F W., Brink, W R., Houser, H B. Hahn E. O. & Di le, J H Amer J Med. 10·673, 1951
Ward H Med. J Aust 1:208, 1956.
Watson T. Cited by Wilson, M. G 1940.
Wearn J T., Bromer, A. W & Zschiesche, L. J Amer Heart J 11:22, 1936.
Wells, W C. Cited by Wilson, M. G 1940.
Wenkö L., B örck, G., Grafoo d C., Wulff H., Kroon, H & Eliasch H Amer Heart J 45:477 1953.
Wertman, C. Social-med. T 27:26 1950.
White, P D Heart disease 4. ed., The Macmillan Company New York, 1951
— J Amer med. Ass. 152:303, 1953.
White, P D & Jones, T D Amer Heart J 3:302, 1928.
W lcox W F Biomet Bull. 1 60, 1945.
Willius, F A. Amer Heart J 3:139 1927
Wilson J K. & Greenwood W F Canad. med. Ass. J 71:323, 1954
Wilso M G. Rheumatic fever Studies of the epidemiology manifestations, diagnosis nd treatment of the disease during the first three decades. Commonwealth Fund London, 1940.
Wilso M G Lim W N & B uch, A. M J chron Dis 7 183, 1958
Wilson, M G & Lubschez, R. J Amer med. Ass 126 477 1944
Winblad S. Acta path. microbiol. scand Suppl 44 1941
Winblad S Ma mon, H & Wila der, O Act med scand Suppl 196, 1947 p 333.
— Acta med scand 133 358, 1949
W ler G J Amer med Ass. 145:719 1951
Wood P Brit med. J 1 1051 1954.
— Amer J Cardiol. 1 553, 1958
— Diseases of the heart and circulation. 2. ed. J B Lippincott Company Philadelphia, 1956
Wulff H B. Biörck G Ber a, N. P Kroon, H Axén O & L ndergo O Acta med. scand. 144 275, 1953
Zapfe, H & Nemes, M Ärztl. Wschr 14:479 1959

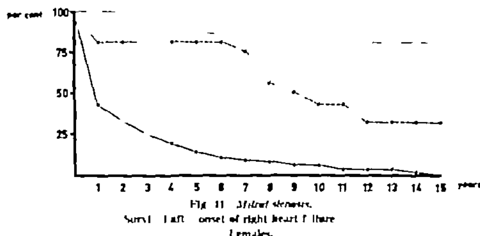


Fig. 11. *Mitral stenosis.*
Surv l l aft onset of right heart f ilure
Females.

——— utopsy series (1(I cases)
o o clinical series (38 cases)
+ + operated series (26 ses)

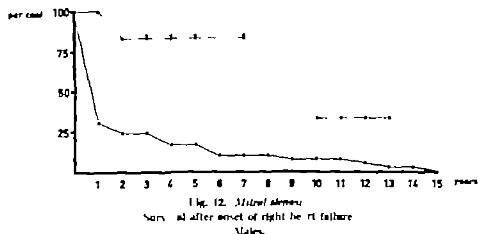


Fig. 12. *Mitral stenosi*
Surv al after onset of right he rt failure
Males.

——— autops series (12 ases)
clinical series (6 cases)
+ operated series (7 cases)
(Series not strictly comparable)

mean age t the time of death was somewhat higher than i the utopsy series. The nalysis also shows that direct comparison between th operated series and the ther two gro ps is not possible because they differed both in frequency of A R.F and in age at the time f the first symptoms et

I the evaluation of any conclusions uggested by the following analysis it should be stressed that the series under iscussion — autopsy clinical and operated series — are not strictly comparable According to DONZELOT et al. (1958), ELLIS, HARKEN & BLACK (1959) and BANNISTER

RESULTS AND COMMENTS

The present analysis of rheumatic valvular heart disease is based on a series of patients admitted to Malmö General Hospital during the period 1930—54. The archives of the departments of paediatrics (including Ronneholms Clinic), infectious diseases, orthopaedics and medicine were searched. The material includes all cases with a firm or doubtful diagnosis of rheumatic valvular disease. Patients who were not residents of Malmö at the time of admission as well as patients with firm or doubtful diagnosis of congenital heart disease and patients with syphilitic aortic lesions were excluded. Since the town of Malmö has only one hospital (no private hospitals) it may be assumed that the material studied is representative of the population.

Any clinical series covering such a long period must have some inherent sources of error. The clinical evaluation and criteria for the diagnosis of rheumatic heart disease (R.H.D.) have certainly changed, and as mentioned in Part I the evaluation of the auscultatory findings, particularly apical systolic murmurs has changed. The diagnostic adjuncts have been refined and roentgen graphy and electrocardiography have been used more frequently.

It might be objected that it would have been better to limit the series to those cases in which the diagnosis could be considered as firm according to the criteria set up by New York Heart Association (N.Y.H.A.), but as in acute rheumatic fever (A.R.F.) this would imply the exclusion of patients with R.H.D.

In the beginning of Part II an account is given of the clinical material (diagnoses of pure mitral, mitral and aortic, pure aortic and non-specified valvular lesions, and the age at the time of first admission). All patients with the above mentioned diagnoses were accepted irrespective of any later revision. Mitral lesions were found to be so much more common than aortic lesions, as to suggest an over-diagnosis of mitral lesions or an under-diagnosis of aortic lesions. The age at the time of first admission was high, and of patients with M.S. and M.S.M.I. 43.4 per cent of the females and 37.7 per cent of the males were as old as 50 years or more. Analysis of the total material suggested that R.H.D. was becoming less frequent.

In order to secure comparable groups for various 5-year periods, and since it might be claimed that the reduction in the number of cases diagnosed may be due to modifications and improvements in diagnostic methods, the patients were divided into three groups according to the firmness of diagnosis (See Chapter on Definitions"). The clinical data available on 4 or 2.6 per cent out of 1 740 patients of the entire material were incomplete and 985 (58.1 per cent) were judged as firm according to the criteria by N.Y.H.A., 432 (25.5 per cent) as probable and 278 (16.4 per cent) as suspected. The frequency of a firm diagnosis per 10 000 inhabitants per year in the various 5-year periods was 1930—34 2.7, 1935—39 2.3, 1940—44 2.4, 1945—49 2.6 and 1950—54 2.0. There was, thus, no decrease until 1950.

At the first glance it might be tempting to ascribe this decrease to the opening of a special heart laboratory in 1951 or to the change in the directorship of the department of internal medicine between the

Of the total material of R.H.D. except A.S. a significant improvement (1 — 0.001) was found for those without A.R.F. in the history but not for those with. It is noteworthy that in patients with A.R.F. the mean age at the onset of heart symptoms was largely the same in all the 5-year periods, while in the group without A.R.F. in the history the mean age at the onset of heart symptoms, like the mean age at death, steadily increased. This gives rise to the question whether all cases of R.H.D. are of a single aetiology.

The improvement of the prognosis was judged on the basis of all patients who had died in hospital or at home (no difference in the mean age at death). The prognosis of R.H.D. in general appeared to have improved, except for patients with aortic stenosis.

The prognosis of A.S. has not changed during the investigation period and the mean age at death was 66.9 years for females and 60.0 for males. The duration of survival from the onset of first heart symptoms and the first attack of right heart failure in patients with A.S. agreed largely with figures given in the literature (Fig. 32 and 33). The mean age at death for patients with M.S.M.I. and M.I. was somewhat lower, namely 52.3 and 49.8 years.

A report of patients operated upon for mitral stenosis — probably including some less severe cases than other series on record — is followed by a description of the natural history (Figs. 37—42). The mean age at death in patients with M.S. was 7 years for females and 48.8 years for males in the autopsy series, and the corresponding figures in the clinical series were 48.2 and 9.0 respectively. The survival rate from the first attack of A.R.F., the first heart symptoms and right heart failure is given for the autopsy, clinical and operated series. The series are not strictly comparable, but as long as the survival rate for the operated series compares favourably with that for the series treated conservatively there is reason to consider operation in properly selected cases, even though the benefit of surgery is prone to wear off after 6—8 years. The prognosis of M.S. after right heart failure improved during the latter part of the investigation period, which may be ascribed, in some measure, to surgery and to new therapeutics.

SUMMARY

Malmö is one of the few towns in the world that is really suitable for epidemiological investigations because the town has only one hospital and that hospital caters for a population of more than 200 000 inhabitants. This advantage was therefore utilized to study the natural history and the prognosis of rheumatic heart disease. The hospital records and parish registers were studied for the subsequent course of patients with rheumatic heart disease admitted to Malmö General Hospital in 1930—51 and representative groups of the survivors were reviewed in 1953 and later.

A general survey is first given of all patients with rheumatic heart disease admitted to the hospital during the years 1930—51. These cases are analysed and grouped according to firmness of diagnosis, and the future frequency of rheumatic heart disease is predicted on the basis of the frequency of acute rheumatic fever (Part I) and the frequency of rheumatic heart disease. A comparison between an autopsy and a clinical series showed largely good agreement, with a possibly slight under-diagnosis of aortic stenosis in the clinical series. Analysis of the natural history of rheumatic heart disease revealed an improvement of the prognosis. The operated series of mitral stenosis is briefly described and the further course of the patients is elucidated against the background of the series treated conservatively.

Below the observations made in the

REFERENCES

AASTR H. L. Prognoseet tler el kronhk hjertefidelser med benbhk paa lektrokardiogrammernes prognostisk betydnl g. Ejnar Munksgaard forlag, København, 1937 p. 131.

A STR T H. & PTTERSEN K. B. Acta med. scand Suppl. 266 1952, p.147

American Heart Association, 1953 see Jones criteria (modified).

America Rheumatism A sociation, 1937 see Rores et al. 1937

American Rheumatism Association, 1939 see Rheumatism d Arthritis, 1939

A DYBSO M W., KELS T J R. J & EDW RDS, J E. J Amer med. Ass. 149 9 1952.

A SCHUTZ, F Rheumatische Herzklappenfehler In: Die Prognose hronischer Lr krankungen, Herausgegeben on F Linne weh, Springer Verlag, Berlin, 1960, p. 370.

ANNSE L., BROCH ER-MORTI SEN K & HART B. Act med. scand. 141 77 1951

AR DSSO H. Acta radiol., Suppl. 158 1958.

ASH R Amer Heart J 36.89 1948

ATW TER, R. M Amer J Hyg. 7.343, 1927

B CH I H LL, N G., PRESTON T W & THO TON, C. E. Ann rheum. Dis. 1:210, 1939

B CK, F H & DEPASS, E. E. W Indian med J 6.93, 1937

B DEN H Surgical treatment of mitral tenosis. Store Nordisk Videnskabsboghandel, Copenhagen, 1959

BAILEY C. P Surgery of the heart. Henry Kingston, London, 1955.

BAKER C. Advanc intern. Med 10.13, 1960.

BAKER, C. BROCK, R. C., CAMPBELL, M. & WOOD, P Brit. med. J 1 1013, 1952.

B KER, L. A SPR OCK, H. B & WHITE, P D Amer J med. Sci. 206:31 1943.

BALLON US, G (GUILLAUME DE BAILLO): Cited by Wilson, M. G., 1940.

BANNISTER R. G. Lancet 2:329, 1960

BARLOW T & WARNER, F Cited by Wilson, M G 1940.

B UER, W CLARK, W S. & KULKA, J P Ann. rheum. Dis. 10:470 1951

BEDFO P D & CAIRD, F L. Valvular disease of the heart in old age J & A. Churchill, Ltd., London, 1960.

B BIE, J Cited b Jacobsson, L. 1946

BERNFRO J ABELM N W H., VARQUEZ M LA H & ELLIS, L. B. Arch. I tern. Med. 91.911 1953

B KSON J & G E, R. P Proc. May Clin. 25 270, 1950.

BER STEIN L. & BROCH O J Acta med scand 133:183, 1949

BJORCK, G. Cardiologia 23:21 1953

— J chron. Dis. 1.591 1955.

— Amer Heart J 58.414 1959

BJ RCK, G., A N O., KROOK. H., A DRÉN L. & WULFF H. B. Amer Heart J 45.13 1953.

BJ CK, G A É O WULFF H B., LUNDSKOG, O KROOK, H & BÜLOW K. Acta med. scand. 151 19 1955

BJORCK, G & HALL, P Acta rheum. scand. 1 119 1955.

BJÖ CK, G WINBLAD S. & WULFF H. B. Amer Heart J 44.325, 1952

BLAND, E. F & J ES, T D J Amer med. Ass. 113:1380, 1939

— Circulation 4.836 1951

— Ann. intern. Med. 37 1000, 1952.

BLA D, E. F WHITE, P D & JONES, T D Amer Heart J 10:995, 1935

BOUILLAUD, J B., Traité clinique du rhumatisme articulaire, et de la loi coïncidence des inflammations du coeur avec cett maladie J B. Baillière Paris, 1840.

BRIGDE W & LEATH M, A. Brit. Heart J 15.55, 1953.

BRI NT R. Cited by Wilson, M. G., 1940.

BROWN M. G & W LFF L. New Engl. J Med. 223:242, 1940.

B NO, F E. & E ELM DT H. T New Orleans med. surg. J 65 234 1912.

BUND W E., MCCUE, C. M & PORTER, R. R. J Pediat. 41.320 1952.

BU CHELL, H. B., KLAKEG, C. H., PRUITT R. D & BERKSO J Cardiologia 24.129, 1954

B LOW K., BJ RCK, G., AXÉN O., KROOK, H., WULFF H. B. & WINBLAD S. Amer Heart J 50:242 1955

BYW TERS, E. G. L. Brit. Heart J 12:101 1950

BYW TERS, E. G. L. & THOMAS, G. T Brit. med. J 2.350, 1958.

Hämeen Kirjapaino Oy 1961
Tampere — Finland

JACCOUD, J. S. Leçons de Clinique Médicale l'Hôpital de la Charité. 2. ed. 1869.
JOHNSSON, I. Acta paediat. Suppl. 63, 1946.
— Acta paediat. 38:371, 1949.
J NTARY L. E., BED LL, C. N. THAYLER, L. O. & W LD J. B. J. Jow St med. Soc 4 18 1937.
J N T. D. J. Amer med. Ass. 126:481 1944.
Jones criteria (modified) for guida ce in the diagnosis of rheumatic fever. Mod. Conc cardio. Dis. 24:291 1955.
JONSELL, S., Acta radiol. 20:325, 1939.
J N SO J. Acta rheum. scand. 6 3, 1960.

KALBAK, K. Experimentelle og kliniske under- søgelser over O-streptolysin og forekomsten f O-antistreptolysin i serum, med saerlig henblik paa forholdet ed pol rthriti acuta. Ejnar M nk gaard forlag, Køben havn, 1942.
KARLSTRÖM, I. Nord. Med. 8:2633, 104.
KARS FR, H T & K LTER S. Calcific disease f the aortic alv. J. B. Lippincott Com pany. Philadelphia, 1947.
KERLEY, C. D. Lancet 1:1206 1934.
KIRK, A. Act med scand. Suppl 236 1949.
KJØRST o H. Acta med scand. 155:337, 185.
KNOWELDE, J. Brit. J soc Med 3:2 1949.
KUMP, C. W. & H W. B. Medicine 27:13 1948.

LEATH M. A. Lancet 2. 03, 1958.
— Lancet 2:73 1938.
LEVY S. Ann. rheum. Dis. 13:33, 1 54.
LEV CK G & SCHLES ER, M. J. Ame Heart J 18:43 1939.
L K, S. A. & HAR EY W. P. Clinical aus- cultation of the heart. W. B. Saunders Compan Philadelphia, 1949.
LEWES D. Brit med J 1:211 1951.
LEW S-J SO J. Acta paediat. Suppl. 76 1949.
LILJESTR D C L AR E N LIN G & ZACHARISO C G. Amer Heart J 17:406, 1939.
L RSO E. Personal communications.
LOOA A & T RR, R. Lancet 1:1 07 1953.
LYSHOLM E. Nylin, C. & QUAR N, K. Acta radiol 15:237 1934.
LO ERN S. Acta med scand. Suppl 174 1946.
— Acta med scand 145:421 1953.

MACAIE, T. T. Amer J med Sci 172:189 1926.
— Amer. Heart J. 3:31 1927.
MADSEN, T. & KALBAK, K., Acta path. microbiol scand. 17:305 1940.
MAHL, G. E. & OXGARY, E. S., J. Amer med. Ass. 166:2127 1958.
MASSELL, B. F. FYLER, D. C. & ROY S. B. Amer J. Cardiol. 1:436, 1958.
MASSELL, B. F. & JONES, T. D. Amer Heart J 27:575 1944.

M CREA, C. NYLI C & SOLLBERG R, A. Acta cardiol. 10:336, 1955.
MCCARTY M. Bull. rheum. Dis. 7:3, 195.
— Circulation 14:1135 19 6.
MCCUE, C. M & G N, L. F. J. Pediat. 33:46 1948.
MCGIN S & WHITE P D. Amer J med. Sci 188:1 1934.
Medical Research Council of Great Britain and the American Council on Rheumatic Fever 1955, see Treatment of acut rheumatic fever in hildren.
MITCHELL, A. M. S ck. ty C. H. HENDRICKS W. J. & LEV E, S. A. Amer. Heart J. 48:684, 1954.
MITCHELL, J. J. Louisian med. Soc 107:68 1955.
MORTIMER, E. A. JR., A SM S. A A G SCH J. SCH STER. A. R NTA, L. K. R S M RO ERTS, R. & R W KANT C. H. J. New Engl. J. Med. 260:101 1959.
MÜLLER, C. Acta med scand. 156:211 1956.
M CKERERG J. C. A rchow. Arch path. Anat. 176:172, 1904.

New York Heart Association, 1955, see Nomen clature and criteria for diagnosis.
Nomenclature and criteria for diagnosis of diseases of the heart and blood essels. By the criteria committee of the New York Heart Association, Inc. 5 ed. 1955.
N LIN G. Acta med. scand. Suppl. 266 1952, p. 797.

OLESEN, K. H. Mitral stenosis. A follow-up f 351 patients. Ejnar Munksgaards Forlag, Copenhagen, 1955.
OLESEN K. H. & WARB RG E. Acta med. scand. 160:437 1958.
OTTERBECK, W. KROOK, H. & BL ECK, G. Z Kreisl Forsch. 44:22, 1955.

P RK, E. & ELSTER, S. K., Amer. J. Med. 26:421 1958.
PARKINSO J. Lancet 2:837 1945.
P UL, J. R., The epidemiology of rheumati fever and some of its public health aspects. 2 ed. Metropolitan Lif Insurance Com- pany. New York, 1943.
PERRY C. B. Brit. med. J. 2:843 1944.
PITCAIR D. Cited b Wilson, M. G. 1940.

QUIN R. W. & QUINN J. P. New Engl. J Med. 245:211, 1951.

RABOW H. L. & T YLOR, J. S., Amer Heart J 21:244, 1941.
RAMMELKAMP C. H. JR: Circulation 17:842, 1958.
Rheumatism and Arthritis, Review of American and English literature of recent years. Ann. intern. Med. 28:66, 1948.

ACTA MEDICA
SCANDINAVICA

SUPPLEMENTUM 364

DIE HERZINFARKTFREQUENZ

in einem Material der Bevölkerung von Helsinki während der Jahre 1945—1952

von

OLEG GORBATOW

Accompanies Vol. 169

HELSINKI — HELSINGFORS 1961

steigen, und somit erschien es angezeigt, ein hiesiges Material (aus Helsinki) auf Faktoren zu untersuchen, die möglicherweise für die Erklärung des Auftretens von Coronarthrombose Aufschluss geben können.

Es ist nun zwar nachdem vorliegende Untersuchung schon in Vorbereitung war eine Publikation von Linko mit ähnlicher Thematik erschienen, doch ist das von mir in Helsinki gesammelte Material bei weitem umfangreicher und ich habe mich auch bemüht, es eingehender zu behandeln.

AUS DER MEDIZINISCHEN ABTEILUNG DES MARIA
KRANKENHAUSES IN HELSINKI

DIE HERZINFARKTFREQUENZ

in einem Material der Bevölkerung von Helsinki während der Jahre 1945–1952

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Meinem Vater zum Gedächtnis

Deutschland betrifft so schrieben Hochrein und Schneyer (74) 1936 dass der bis dato als Seltenheit bezeichnete Myokardinfarkt immer häufiger wurde. Auch Master Jaffe und Dack (110) diskutierten das Problem i.J 1939 und konstatierten ein markantes Ansteigen der Coronarerkrankungen und der Herzinfarkte während der 30er Jahre In einer Publikation d.J 1941 führten Bland und White (16) die Zunahme der Herzinfarkte u.a. darauf zurück, dass leichtere Fälle nunmehr häufiger als bisher diagnostiziert wurden.

So nennt Master (114) den Herzinfarkt mit 8,5 % aller Todesfälle nach Carcinomerkrankungen die gewöhnlichste Todesursache er betonte dass sich auch unter anderen Diagnosen Herzinfarkte verbergen können und äusserte die Meinung dass bei 25 % aller Diagnosen von Myokarderkrankungen, 60 % der Coronarerkrankungen und in 80 % aller Fälle von Angina pectoris eigentlich mit Herzinfarkt zu rechnen sei. Auch nach ihm ist die Zunahme der Coronarerkrankungsfrequenz mit den Ansteigen der durchschnittlichen Lebensdauer der grösseren Anzahl alter Leute und dem Nachlassen der Infektionskrankheiten zu erklären. Dies würde also besagen, dass die Medizin Fortschritte gemacht hat, dass die Gesundheitspflege verbessert und die Säuglingssterblichkeit gesunken ist, sowie dass eine richtigere und genauere Terminologie eingeführt worden ist. Nach Ansicht dieses Autors ist das enorme Ansteigen der Herzinfarktfälle seit 1930 z.T darauf zurückzuführen, dass man in der Diagnose dieser Erkrankung gerade von besagtem Jahr an Fortschritte gemacht hat. Dieselbe Auffassung äusserte der Schweizer Ott (131) der feststellte dass die Diagnose Hirnschlag und »Altersschwäche» seit dem Ansteigen von Arteriosklerose Herzerkrankungen und Carcinom seltener geworden ist.

Auch der Rapport von Ryle und Russel (150) zeigt eine starke Zunahme der Herzinfarktfälle nachdem die Zahl der Todesfälle an Angina pectoris» in England u. Wales i.J 1926 mit 1880 gegenüber 25 012 Todesfällen an Coronarerkrankungen 1945 angegeben wird.

Wie Morris (120) mitteilt, haben die Fälle der Coronarerkrankungen in England zugenommen (nach Registrar Generals Tab) was jedoch nicht auf einer Verbesserung der Diagnostik oder dem Älterwerden beruhe. Er zeigt eine siebenfache Erhöhung der Coronarerkrankungen zwischen 1944 u. 1949 gegenüber 1907 u. 1914. Scherf und Boyd (152) haben darauf verwiesen, dass diese Erkrankungen auf Grund noch unbekannter Ursachen anzusteigen scheinen.

In seiner Untersuchung über Westaustralien für 1937—1950 teilte Davidson (35) mit dass eine tatsächliche Zunahme der Herzinfarkte seiner Auffassung nach für Männer bei 41—112 % und für Frauen bei 9—52 % liegen dürfte. Die tatsächliche Zunahme sei nicht so gross wie die von den Mortalitätstabellen angegebene. Die Ursache hierfür sei sowohl in den Veränderungen der Diagnosen-Nomenklatur als auch im Älterwer

INHALT

den 15,8 % errechnet — eine Abnahme auf deren mögliche Ursache wir in einem späteren Kapitel eingehen. In einer Arbeit aus dem Gebiet von Norrköping haben Brahme und Ahlberg (24) die Schwierigkeiten hervorgehoben, die mit der Eruierung der wirklichen Frequenz der Herzthrombose verbunden sind, nachdem diese sich unter Diagnosen wie z.B. Myokarditis chronica Myokarditis acuta, Kardiosklerose und Kardioarteriosklerose verbergen können. Ein deutliches Ansteigen der Herzthrombosefälle für die Zeit 1927—1946 konnte ebenfalls in der medizinischen Klinik von Norrköping festgestellt werden. Vor allem muss es auffallen, dass nicht weniger als 29 % des Materials aus den beiden letztgenannten Jahren stammen. Nach Ansicht der Autoren muss die Zunahme darauf beruhen, dass die früher als akute Myokarditis zuhause behandelten Fälle heute immer häufiger und durchaus mit Recht, als Herzthrombosen erkannt werden. Während man geneigt war eine Erkrankung mit der Diagnose akute Myokarditis" zuhause zu pflegen, brachte man den Mut hierfür bei einer akuten Herzthrombose nicht auf. Die Autoren äussern aber dass auch Grund besteht, eine wirkliche Vermehrung der Thrombosefälle anzunehmen.

Im Zentrallazarett von Orebro wurden nach Malmroos (102) vor dem Kriege und während der ersten Kriegsjahre etwa 20—25 Infarktfälle pro Jahr behandelt. Die Zahl der Fälle ist im Verlauf der Jahre ständig gestiegen und betrug 1948 130 Nach Malmroos Ansicht kann es sich durchaus nicht nur um einen scheinbaren Anstieg auf Grund genauerer Diagnosen handeln. In allen von der Statistik erfassten Fällen wurden EKG-Aufnahmen gemacht, auch die herangezogene Nomenklatur wurde im Verlauf der Zeit nicht verändert.

Biörck und Blomquist (12) haben gezeigt, dass einerseits die Totalsterblichkeit in Schweden bei einem Vergleich der Perioden 1911—1915 und 1941—1944 um 25 % gefallen ist, während gleichzeitig die Coronar Sterbefälle um 67 % zugenommen haben nach der offiziellen Statistik bilden die Todesfälle bei Herzerkrankungen etwa 40 % der totalen schwedischen Sterblichkeit.

Ström und Jensen (164) haben eine Zunahme der Sterbefälle bei Myokarditis chron. in Norwegen während der Zeit 1927—1948 nachgewisen. In dieser Diagnose sind auch die Coronarerkrankungen enthalten. Ein Rückgang dieser Erkrankungen wurde während der Zeit 1941—1945 beobachtet.

Die unten abgebildete Kurve (Fig 1) über die Mortalität bei Arteriosklerose und Myokarditis chron. in Stockholm während der Jahre 1928—1949 wurde von Henschen (71) publiziert Wie er betont, verbergen sich unter diesen Diagnosen Coronarer krankungen. Die Kurve zeigt einen steten Anstieg von 1928 bis 1941 und nach Henschens Ansicht beruhte das darauf, dass diese Diagnose immer üblicher wurde. Der starke Rückgang von 1941—1945 ist jedoch kaum darauf zurückzuführen, dass die Ärzte

VORWORT

Den Impuls zu der hier vorgelegten Arbeit verdanke ich dem Chef der kommunalen medizinischen Abteilung des Maria-Krankenhauses zu Helsinki, Herrn Professor Dr med. Guido Tötterman. Ich möchte mir erlauben, ihm auch an dieser Stelle für seine nicht zu überschätzende Hilfe und sein Interesse an meiner Arbeit ergebenst zu danken. Ferner möchte ich meinen ergebenen Dank aussprechen Herrn Professor Dr med. Bertel von Bonsdorff der meiner Arbeit ebenfalls Interesse entgegenbrachte und es mir ermöglicht hat, auch Fälle von der IV Universitätsklinik zu Helsinki—Helsingfors in mein Material aufzunehmen.

Danken möchte ich ferner für eine Vielzahl wertvoller Ratschläge, die ich während der einzelnen Phasen meiner Arbeit entgegennehmen durfte von Herrn Professor Dr med. Pentti Halonen und Herrn Dozent Dr med. Martti Karvonen.

Die statistische Bearbeitung des Materials hat mir Herr Dr rer pol. Tapani Purola abgenommen, dem ich hierdurch meinen Dank abstatten möchte. Die Übersetzung stammt von Herrn Lektor Carl August von Willebrand, die medizinische Terminologie wurde von Herrn Dr med. Jürgen Schumacher geprüft. Auch diesen Herren spreche ich meinen Dank aus.

Es sei mir auch erlaubt, meiner Frau für ihre Hilfe beim Ausarbeiten des Manuskriptes und für ihr unermüdliches ermunterndes Interesse an meiner Arbeit recht herzlich zu danken.

Meine Arbeit erfuhr wertvolle ökonomische Unterstützung durch Stipendien seitens der Finska Läkaresällskapet und der Arzneimittelfirma O/Y STAR A/B

Helsingfors, im Mai 1961.

Oleg Gorbatow

ku für die Jahre 1947—52 mitgeteilt wird. Die Patienten Zahlen waren

Jahr	*Anzahl*	*Jahr*	*Anzahl*
1947	28	1950	65
1948	35	1951	114
1949	66	1952	124

Nach Ansicht des Autors konnte dieses Ansteigen weder der Bevölkerungszunahme, noch der Zunahme der Lebensdauer oder etwa diätetischen Fragen zugeschrieben werden, da der beobachtete Zeitraum relativ wie absolut gesehen kurz ist. Er hat dagegen die Möglichkeit einbezogen, dass während der späteren Jahre auch leichtere Fälle stationär behandelt und dass die diagnostischen Methoden verbessert wurden. So konstatiert er auch, dass 1952 eine etwas grössere Anzahl leichter Fälle in stationäre Behandlung aufgenommen worden wurde, doch ist hieraus die starke Zunahme der Fälle nicht erklärbar Linko ist nicht der Ansicht, dass die Diagnoseverbesserungen mittels neuer EKG-Schaltungen nennenswert auf die Frequenzzunahme eingewirkt haben. Seiner Meinung nach ist die Frage kompliziert und die einwirkenden Faktoren schwer zu beurteilen. v Bonsdorff (21) hat für die Jahre 1936—1940 in Finnland eine Zunahme der Todesfälle an Koronarerkrankungen festgestellt, während für die nachfolgenden Jahre (bis 1943) keine weiteren Zunahmen zu beobachten waren. Auch Varpela (170) hat eine Zunahme der Kranzarterienerkrankungen in Helsinki während der Zeit 1930—1950 gezeigt, jedoch ergab sich ein Nachlassen der Sterblichkeit bei Frauen in der Zeit während des letzten Krieges

Zusammenfassend darf man sagen, dass alle Autoren für die letzten Jahrzehnte eine klare Zunahme der Herzinfarktfrequenz festgestellt haben, ohne allerdings über die Grundfaktoren dieser Zunahme einer Meinung zu sein.

Sterblichkeit, Alter und Geschlecht

Die Forscher sind alle der Meinung dass die Frequenz der Herzinfarkte sich erhöht hat und geben verschiedene Ursachen an. In einem Punkt herrscht Einmütigkeit — leichtere Fälle werden heute häufiger als früher diagnostiziert. Hervorgehoben wird ferner die verbesserte Therapie Unter diesen Verhältnissen wäre ein merklicher Rückgang der Sterblichkeit zu erwarten. Es wurden deshalb die Mortalitätsziffern verschiedener Autoren in einer Tabelle zusammengestellt. Die Zahlen können jedoch nicht immer ohne weiteres miteinander verglichen werden, da sie aus unterschiedlichem Material stammen — es mussten Untersuchungen über einen Zeitraum von 10—20 Jahren, aber auch solche für nur ein Jahr berücksichtigt werden. Ausserdem mussten Spezialfälle wie die Arbeiten von Yaters (186) und Newmans (126) herangezogen werden.

Der Mortalitätsprozentsatz der einzelnen Materiale variiert in der Tabelle in hohem Masse. Ausser dem

I EINLEITUNG

Bei den Krankheiten die seit historischer Zeit als eine Geissel der Menschheit aufgetreten sind, lassen sich sowohl ihrer Frequenz wie ihrer Art nach starke Veränderungen beobachten. Mit dem erhöhten sozialen Standard und der Erweiterung der medizinischen Kenntnisse sind manche Krankheiten so gut wie völlig verschwunden und neue haben die Statistiken erobert. So gehören Pest und Spital in Europa der Vergangenheit an die Syphilis die nach den Schilderungen aus dem XV u. XVI Jh. einst eine überaus verbreitete akute Krankheit war ist immer seltener und zu einer chronischen Erkrankung geworden. Aber auch die Bedeutung der Infektionskrankheiten hat sich in den letzten zwei Jahrzehnten durch die Einführung der Chemotherapeutika und der Antibiotika wesentlich vermindert Die Tuberkulose hat Jahr für Jahr an Schrecken verloren, und das gilt auch für die Säuglingssterblichkeit

Da die mittlere Lebensdauer in der zivilisierten Gesellschaft steigt ist es natürlich dass Krankheiten, die Menschen vorgerückten Alters befallen, in den Statistiken über Todesursachen immer mehr an Bedeutung gewinnen. An der Spitze stehen hier zur Zeit Herzerkrankungen und Arteriosklerose Bei den Herzerkrankungen stehen die Coronarfälle oben. Die Krankheiten haben während der letzten Jahrzehnte beunruhigend zugenommen und scheinen immer jüngere Jahrgänge zu befallen. Die starke Zunahme hat das Interesse vieler Forscher erregt und es besteht nunmehr recht allgemein die Auffassung dass hier neben der mittleren Lebensdauer auch andere Faktoren im Spiele sind. Für solche Faktoren hält man u.a. die veränderten Lebensumstände des Menschen.

Die Fragestellung ist bereits in verschiedenen Ländern beleuchtet worden doch ist man nach den Angaben der derzeitigen Literatur bisher noch nicht zu einer vollständigen Klarheit über die Ursachen der rapiden Steigerung der Coronarerkrankungen gekommen. Soweit es sich übersehen lässt ist einer ganzen Reihe von Faktoren ursächliche Wirkung zuzusprechen, und deshalb dürfte das Vorhandensein möglichst umfassender Beiträge von vielen Seiten für die Klarstellung der Frage von besonderem Wert sein.

Auch in Finnland zeigten die Coronarerkrankungen während der vergangenen Jahrzehnte ein starkes An

Gordin (keine antikoagul. Behandlung) (57) [1]	1953	71	126
Gordin (antikoagul Behandlung) (57) [1]	1953	3,2	126
Ekvall (48)	1955	31,9	232
Westlund und Hougen (174)	1956	42 4	1613
Järvinen (82)	1960	20	133

Die Mortalität von Herzinfarktpatienten nach dem Material verschiedener Autoren.

Wie Järvinen gezeigt hat (82) strengen sich finnische Männer nach Auftreten des Anfalles häufig physisch an und das kann schwerwiegende Folgen haben. Nach Brahme und Ahlberg (24) können Unterschiede sich daraus herleiten, dass leichtere Fälle gelegentlich auch zuhause behandelt werden. Auch nach Helanders Ansicht (69) ist die grosse Verschiedenheit der Mortalität auf die Unterschiedlichkeit des Materials und die Behandlung zurückzuführen. In den Teilen des Materials die einigermassen vergleichbar sind kann indessen ein wirklich starker Mortalitätsrückgang während der letzten Jahre nicht beobachtet werden. Nach dem Material von Biörck (13) betrug die Mortalität i.J 1934 43 % gegenüber 37 % für 1953 d.i. also ein Rückgang von nur 6 % Die Frequenz weist demgegenüber eine Zunahme von 377 % auf das Material umfasst nämlich sämtliche im betr Krankenhaus während der angeführten Zeit behandelte Infarktfälle. Zu ähnlichen Zahlen gelangt Ekvall (48) Im Zentralkrankenhaus von Umeå wurden 1939 9 Patienten mit Coronarinfarkt behandelt, von denen 2 verstarben. 1950 verstarben dagegen 17 von 46 behandelten Fällen — somit war die Mortalität nun prozentual höher als 1939 Für eine statistische Auswertung sind diese Zahlen allerdings zu klein.

In Zusammenhang mit der Mortalität tritt die Frage des Alters beim Herzinfarkt auf Es wird ja allgemein angenommen, dass heutzutage bedeutend mehr Menschen als früher das sog. Herzinfarktalter erreichen und hierauf wird die grosse Frequenzzunahme zurückgeführt. Diese Behauptung ist nun allerdings cum grano salis zu nehmen, denn das hohe Durchschnittsalter der Bevölkerung beruht, wie die Bevölkerungsstatistiker zeigen weniger auf einer Vergrösserung der älteren Jahrgänge sondern auf dem Rückgang der Säuglingssterblichkeit. Das Durchschnittsalter der Herzinfarktpatienten liegt nach dem Material der meisten Forscher zwischen dem 55 und dem 65 Lebensjahr Dieser Durchschnitt zeigt sich im Material folgender Forscher:

Levine und Brown (93) Conner und Holt (33) White und Bland

[1]) Das Material verzeichnet nicht Sterbefälle die innerh. von 3 Tagen nach Aufnahme eintraten

II DAS SCHRIFTTUM

Frequenzzunahmen der Coronarerkrankungen

William Heberden (67) dürfte als erster die Angina pectoris beschrieben haben, und zwar publizierte er im Jahre 1768 20 Fälle. 1782 verfügte er bereits über ein Material von 100 Fällen. Eine Volkskrankheit jedoch war die Angina pectoris in England weder damals noch später, etwa im Jahre 1925, als Mackenzie (101), einer der führenden britischen Kardiologen, mitteilte, das insgesamt 380 Patienten ihn wegen Angina pectoris konsultiert hatten. Während der folgenden Jahrzehnte ist die Frequenz stark angestiegen, und 1946 schrieb Cassidy (29), dass der moderne britische Kadiologe seine Patienten nicht nach Hunderten, sondern nach Tausenden zählt. In den Statistiken der USA spielte der Herztod zu Beginn unseres Jh. noch keine bedeutendere Rolle; nach den Angaben von Albert (2) aus dem Jahre 1927 kamen in den USA 1900 132 Fälle von Herztod auf 100000 Einwohner, und da nur ein Teil dieser Fälle auf das Konto von Coronarinfarkten kam, kann man verstehen, wie unbedeutend diese Infarkte damals in den Statistiken waren. Wespi (173) hat darauf hingewiesen, dass in Guttmanns Medizinischer Terminologie (1927) das Wort «Herzinfarkt» nicht vorkommt, während der Herzinfarkt in Friedbergs *Diseases of the Heart* als die gewöhnlichste Todesursache in den USA bezeichnet wird.

Nach den meisten neueren Publikationen über den Herzinfarkt hat sich diese Krankheit während der letzten zwanzig Jahre stark ausgebreitet. Albert (2) betonte schon 1927, dass die Anzahl der Herzerkrankungen im Verlauf von 1900—1925 um ca. 42 % zugenommen habe. Die Ursache erblickte er in der längeren Lebensdauer, wodurch der Mensch das "Herzerkrankungsalter" erreiche.

Eine völlig neue Frage stellt die Frequenzzunahme des Herztods somit nicht dar, doch ist das Problem durch den starken Anstieg während der vergangenen zwanzig Jahre aktualisiert worden. 1933 stellten Fitzhugh und Hamilton (51) fest, dass die Coronarerkrankungen in den USA zunahmen, was ihrer Meinung nach darauf beruhte, dass immer mehr Menschen das «Angina Pectoris-Alter» erreichten. Ein Jahr später äusserten Riesman und Harris (143), dass die Herzerkrankungen von 1921 bis 1932 zugenommen hatten. Was

Alter abhängt, sondern von der Art des Falles und dass ältere Menschen schwereren Infarktanfällen ausgesetzt sind. Ein gewisses Erstaunen muss jedoch die hohe Mortalität in zwei Arbeiten hervorrufen, die sich ausschliesslich mit Infarkten junger Leute befassen, nämlich bei Yater (186) und Newman (126) (s. Tabelle 1)

Es wäre, wenn als eine der Ursachen der Frequenzzunahme von Infarktfällen die erhöhte durchschn. Lebensdauer genannt wird, anzunehmen, dass auch das durchschn. Lebensalter der Infarktpatienten sich erhöhen würde. Nach einem von Brahme und Ahlberg (24) über die Jahre 1927—1946 ausgewerteten Material ist eine solche Veränderung des Durchschnittsalters von Herzinfarktpatienten nicht eingetreten. Das Material von Ryle und Russels (150) umfasste die Jahre 1921—1945 und dies wie auch das Material von Linden (95) über die Jahre 1942—1951 und das Material von Linko (97) für 1947—1952 gibt das gleiche Resultat. In dem Material von Biörck u.a. (13) über das Durchschnittsalter von Herzinfarktpatienten zeigt sich für 1934 ein Schnitt von 57 J., für 1953 dagegen von 64 J Ekvalls Publikation (48) zeigt, dass während der Zeit von 1939—1948 weniger Infarktpatienten über 60 J aufgenommen wurden, als in den Jahren 1949—1950 Westlund und Hougen (174) hatten die Altersgruppen der 40—59jährigen und der 60—79jährigen für den Zeitraum 1935—1949 untersucht, wobei sich eine Verschiebung zur älteren Gruppe ergab.

In den meisten Aufstellungen über Herzinfarktfälle sind Sterblichkeit und Alter mit einem weiteren Faktor verbunden, nämlich mit dem Geschlecht des Patienten. Es ist eine bekannte Tatsache dass Männer dem Infarkt viel häufiger ausgesetzt sind als Frauen. Eine weitere Aufgliederung des Materials in den Fällen, wo der betr Autor nach Geschlechtern geschieden hat, dürfte allerdings hier zuviel Raum beanspruchen. Ausser dem müsste man hierbei noch das prozentuale Verhältnis Männer Frauen für den Ort der betr Erhebungen einbeziehen. In "Correlative Cardiology bezeichnen Shaffer und Chapman (158) die Männer als klar prädisponiert für Coronarerkrankungen und geben ein Verhältnis von 3—4 1 (Männer Frauen) an. Zu diesem Ergebnis sind auch die meisten anderen Forscher gelangt. Ungefähr dasselbe Verhältnis zeigt das Material der folgenden Forscher· Levine und Brown (93) White und Bland (176) Hochrein und Schneyer (74) Master Dack und Jaffe (112) Parker (134) Cassidy (29) Master (114) Ryle und Russell (150) Rääsänen (151) und Ekvall (48) Eine noch stärkere männliche Dominanz zeigt das Material von Conner und Holt (33) Appelbaum und Nicolson (5) Woods und Barnes (183) Munck (124) und Järvinen (81) Weniger markant, wenn auch durchaus deutlich war die männliche Dominanz im Material von Jervell (78) Bean (7) Rosenbaum und Levine (147) Chambers (31) Brahme und Ahlberg (24) Mintz und Katz (119) Helander (69) Billings u.a. (11) Wällgren

den der Bevölkerung zu suchen. Zu unterscheiden sei zwischen dem wirklichen pathologischen Herzinfarkt und der Coronar Insuffizienz in hohem Alter

Gordon (59) hat mitgeteilt, dass die Mortalität bei arteriosklerotischen Erkrankungen in den Jahren 1940—1951 sich in England verdreifacht hat während Oliver und Boyd (130) äussern, dass die Zunahme in Schottland von 1937—1953 das Vierfache betrug

Bei ihrer Publikation der Resultate von 500 bei Obduktionen verifizierten Infarktfällen i.d.J 1910—1954 konstatieren Lee und Thomas (91) für 1945—1954 eine zwanzigfache Erhöhung der Infarktfälle gegenüber 1910—1919

Die Mortalität bei Coronarinfarkt hat nach Martin (104) in England und Wales während der letzten 15 Jahre um das Zwei bis Dreifache zugenommen auch Miller u.a. (116) haben festgestellt dass die Coronarerkrankungen in den USA von 1900 bis 1955 gestiegen sind.

Nach Winter (180) hat die Mortalität an Coronarerkrankungen i.d.J 1945—1950 in der DDR zugenommen. Gramm (60) meint, dass die Todesfälle bei Blutkreislaufkrankheiten nicht zugenommen haben.

Nach einer Publikation von Hipsley (73) haben in Australien die Sterbefälle an Coronarerkrankungen zwischen 1940 u. 1949 in ausserordentlich hohem Grad zugenommen.

Wie Banst (6) mitteilt, gab es an einer Hamburger Klinik i.J 1949 21 Herzinfarktfälle 1956 dagegen 317 Fälle.

Trotz aller Verbesserungen der Diagnostik verbleiben zweifellos noch immer nicht wenige Herzinfarktfälle unerkannt. So teilten Johnson u.a. (80) i.J 1959 mit dass in einem Obduktionsmaterial von insgesamt 1267 Fällen 143 Herzinfarkte, und zwar sowohl akute wie geheilte, gefunden wurden. Bei den geheilten Fällen handelte es sich zu 50 % um bisher undiagnostizierte Fälle

In seiner Übersicht hat Kappert (83) darauf hingewiesen, dass die Herzinfarktfälle sich in bestimmten europäischen Ländern von 1930—1950 verfünffacht haben.

Das Problem der zunehmenden Herzinfarktfrequenz gewann in den nordischen Ländern gegen Ende der vierziger Jahre Aktualität. Anlässlich eines Diskussionsbeitrages berichtete Ejrup (48) i.J 1943 in der Svenska Läkaresällskapet (Schwed. Ärzteverband) dass die Anzahl der Infarktdiagnosen von 1930—1942 im Krankenhaus "Sabbatsberg" von 0 auf 40 gestiegen war Die Jahreszahlen mit entspr Infarktdiagnosen lauten wie folgt

1930	0	1934	4	1938	6
1931	0	1935	7	1939	13
1932	0	1936	7	1940	23
				1941	31
1933	0	1937	6	1942	40

Für Dänemark wird von Munck (124) berichtet, dass der Herztod i.J 1921 rd. 10 % aller Todesfälle umfasste, während die entspr Zahl für 1940 17,5 % betrug. Für 1943 wur

nterschiedliches Bild ergeben. Eine Eindeutige Verminderung der Mortalitätsätze lässt sich trotz verbesserter Therapie und Diagnostik während der vergangenen Jahre nicht feststellen. Was das Alter betrifft, so sind die Autoren einmütig der Ansicht dass ein Auftreten unter dem 40 Lebensjahr selten ist. Das Mortalitätsalter ist etwas höher als das allgemeine Durchschnittsalter der Coronarinfarktpatienten der Sterblichkeitsprozentsatz steigt mit dem Alter Im Zusammenhang mit dem höheren Durchschnittsalter der Bevölkerung und der zunehmenden Infarktfrequenz während der letzten Jahre wäre man geneigt, auch eine Verschiebung des Durchschnittsalters der Infarktpatienten anzunehmen. Eine derartige Verschiebung ist indessen nur von einem Teil der Autoren festgestellt worden. Was das Geschlecht betrifft so herrscht männliche Dominanz, und zwar ganz besonders ausgeprägt in den jüngeren Jahrgängen während einzelne Forscher bei späteren Jahrgängen weibliche Dominanz angeben.

Zum Zeitpunkt der Erkrankung

Die Jahreszeiten, zu denen der Herzinfarkt aufgetreten ist, haben das Interesse verschiedener Forscher angeregt. Nach Wood und Hedley (182) traten von 133 Fällen 47 im Winter 26 im Frühling 12 im Sommer und 48 im Herbst auf. Nach Master u.a. (109) ereigneten sich 51,3 % der Fälle zwischen Oktober und April gegenüber 48 7 % zwischen April und Oktober Das Material von Bean (7) weist für Herbst, Winter und Frühling ungefähr gleichviele Fälle auf dagegen im Sommer entschieden weniger In einer späteren Untersuchung von Bean (8) treten die meisten Fälle zwischen Januar und April auf. Nach der Erklärung von Bean und Mills (9) war die Ursache für die Häufung der Infarktfrequenz in den nördlichen Gebieten der USA während des Winters die stärkere Infektionsfrequenz und der erhöhte allgemeine Stoffwechsel während dieser Jahreszeit Munck (124) berichtete 1946 dass die meisten Todesfälle bei Herzleiden in Dänemark während der Wintermonate auftraten. Mintz und Katz (119) kamen in einem Material über amerikanische Juden zu dem selben Resultat. Yater u.a. (186) haben für die südl. Gebiete der USA eine etwas erhöhte Sommer Frequenz der Herzinfarkte festgestellt. Billings u.a. (11) haben ein Material von 240 Fällen publiziert, das sich zeitlich wie folgt verteilt

I.	Quartal (Dez.—Feb)	=	30 %
II.	Quartal (März—Mai)	=	22 %
III	Quartal (Juni—Aug)	=	20 %
IV	Quartal (Sept.—Nov)	=	28 %

Ströder u.a. (163) haben gezeigt dass 87,3 % der Herzinfarkte bei Witterungsstörungen auftraten diese Autoren geben das Verhältnis von Sonneneruptionen zu Infarkten an. Jacobs (76) konnte saisonale Zusammenhänge aus seinem Material nicht eruieren. Nach der Arbeit von

vom Gebrauch dieser Diagnose Abstand genommen hätten, sondern darauf, dass diese Erkrankungen in der fraglichen Zeit tatsächlich seltener aufgetreten sind. Die möglichen Ursachen dieses Rückganges werden unten noch zu betrachten sein.



Fig. 1. Die Mortalität bei Arteriosklerose und "Myokarditis chron." in Stockholm während der Zeit 1925—1949 nach der amtl. Statistik. Autor Henschen.
Breite Kurve = relative Zahlen
Dünne Kurve = absolute Zahlen

Im Akademischen Krankenhaus zu Upsala sind von 1942—1951 544 Herzinfarktfälle behandelt worden. Publiziert wurde dieses Material von Linden (95) Auch hier ersieht man eine deutliche Zunahme der Fälle — 1942 24 Fälle, 1951 79 Fälle und ein Maximum von 86 Fällen LJ 1949 Lindhart (96) hat darauf hingewiesen, dass die Herzsterblichkeit bei jüngeren und mittleren männlichen Jahrgängen in Dänemark von 1921 bis 1950 eine Zunahme aufweist. In einer grösseren Arbeit über den Herzinfarkt hat Ekvall (48) u.a. konstatiert, dass ein deutlicher Anstieg von Infarkten in der Praxis des Zentralkrankenhauses von Umeå für die Jahre 1939—1950 festgestellt wurde während 1939 nur 9 Fälle auftraten, waren es 1950 46 Fälle. Ein Nachlassen der Infarktfälle konstatiert auch Ekvall für die Jahre 1941—4..

Biörck, Overbeck und Grönvall (13) konstatierten im Allgem. Krankenhaus von Malmö eine starke Zunahme von Koronarerkrankungen und Infarkten — 1934 30 Infarkte, 1953 143 Infarkte. Wenn auch ein Teil dieser Zunahme anderen Faktoren zugeschrieben werden kann, äussern die Autoren die Ansicht, dass immerhin eine echte Verschiebung eingetreten ist.

Eine Arbeit über Herzinfarkte in Osloer Krankenhäusern von Westlund und Hougen (174) zeigt eine sehr bemerkenswerte Zunahme — gegenüber 24 Fällen LJ 1935 traten LJ 1949 nicht weniger als 233 Fälle auf. Auch Hansen (66) hat für Oslo ähnliche Feststellungen gemacht.

Nach Mattila (117) beliefen sich die Todesfälle durch Herzerkrankungen in Finnland LJ 1927 auf 8 % sämtlicher Todesfälle, hatten aber bis 1956 schon 44 % erreicht. Der Autor war der Ansicht, dass diese Steigerung in der Hauptsache auf Abänderungen der Nomenklatur beruhte. Aber auch Noro (128) hat auf eine Zunahme der Herzerkrankungen in Finnland hingewiesen. In Finnland erschien 1954 eine Arbeit über das Auftreten von Herzinfarkten von Linko (9) in der eine starke Zunahme der Fälle in der Innermediz. Abtlg. der Universitätsklinik in Tur-

Genuss kalten Wassers auftrat. In dem von Fitzhugh und Hamilton (51) veröffentlichten Material nimmt physische Anstrengung vor dem Anfall einen wesentlichen Platz ein. Ferner ging oftmals "Stress" oder eine starke Mahlzeit voran, in einem Falle sexuelle Aktivität. Phipps (138) verzeichnet Auftreten bei "Stress in 23 % bei mässiger oder starker Anstrengung in 51 % "nach der Mahlzeit" in 18 % und bei Ruhe oder im Schlaf bei 8 % der Fälle. Bean (7) gibt an, dass 44 von 88 Fällen bei Ruhe oder Schlaf, 44 bei Aktivität auftraten. Nach Master u.a. (109) traten 40 % der Infarktanfälle bei Ruhe oder Schlaf 2,1 % während harter Arbeit auf. Derselbe Autor teilt mit, dass in einem Material von insgesamt 890 Infarktfällen eingetreten sind 22,3 % im Schlaf 31,1 % bei Ruhe, 20,2 % bei geringer Aktivität 8,5 % bei mässiger Aktivität, 15,8 bei Spaziergängen und 2,0 % bei ungewöhnlicher Anstrengung Als mitbeteiligter Faktor wird in 4,3 % der Fälle eine Infektion angeführt. v Bonsdorff (20) hat die Bedeutung von Erkältungen und Infektionen sowie neurogenen, toxischen und alimentären Faktoren betont, ihre Bewertung ist jedoch schwierig Paterson (136) zeigt, dass die Entstehung der Coronarthrombose ein stufenweiser Vorgang ist, bei dem bis zur Occlusion der Coronarlumina gelegentlich mehrere Tage vergehen können. Die der Attacke direkt vorhergehende Aktivität des Patienten ist deshalb von sekundärer Bedeutung. Boas (18) hat 25 Fälle beschrieben, in denen Infarkte nach einem Stoss auf die Präkordialregion des Brustkorbs oder nach ungewohnter körperlicher Anstrengung auftraten und hat in einer weiteren Arbeit (19) mitgeteilt, dass die gewöhnlichsten, den Infarkt auslösenden Ursachen die folgenden sind Überanstrengung, Gemütsbewegung Kälte, zu starke Mahlzeit, doch äussert er dass diese Faktoren bei einem gesunden Herzen keinen Infarkt hervorrufen können. Cassidy (29) und Master (114) haben darauf hingewiesen, dass keine Beweise dafür vorliegen dass der "Stress" des modernen Lebens einen Faktor für die Zunahme der Coronarerkrankungen bilde. Nach Yater (186) traten die Anfälle häufiger im Verlauf von Anstrengung auf als während der Ruhe oder des Schlafes, während demgegenüber nach dem Material von Billings u.a. (11) Infarkte zum überwiegenden Teil während Ruhe und Schlaf eintraten. Kristenson (89) beschreibt 3 Infarktfälle nach psychichem Trauma, Anderson (4) neun Infarktfälle bei Magen und Gallenleiden. Scherf und Boyd (152) waren der Ansicht, dass ein Trauma gegen den Brustkorb und plötzliche körperliche Anstrengung auslösend wirken können. Nach Newman (126) war 'Stress' in weniger als der Hälfte der beobachteten Fälle als Ursache anzusehen. Gertler u.a. (53) weisen darauf hin dass die Aktivität nicht den direkten Anlass für den Infarkt bildet, dass sie jedoch die Entstehung des Infarkts in einem "Coronarherzen" beschleunigt. Nach Jakobs (76) hatten nur 11 Fälle von

vom Gebrauch dieser Diagnose Abstand genommen hätten, sondern darauf, dass diese Erkrankungen in der fraglichen Zeit tatsächlich seltener aufgetreten sind Die möglichen Ursachen dieses Rückganges werden unten noch zu betrachten sein.

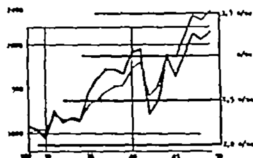


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Biörck Overbeck und Grönvall (13) konstatierten im Allgem. Krankenhaus von Malmö eine starke Zunahme von Koronarerkrankungen und Infarkten — 1934 30 Infarkte, 1953 143 Infarkte. Wenn auch ein Teil dieser Zunahme anderen Faktoren zugeschrieben werden kann, äussern die Autoren die Ansicht, dass immerhin eine echte Verschiebung eingetreten ist.

Eine Arbeit über Herzinfarkte in Osloer Krankenhäusern von West lund und Hougen (174) zeigt eine sehr bemerkenswerte Zunahme — gegenüber 24 Fällen I.J 1935 traten I.J 1949 nicht weniger als 283 Fälle auf. Auch Hansen (66) hat für Oslo ähn liche Feststellungen gemacht.

Nach Mattila (117) beliefen sich die Todesfälle durch Herzerkrankungen in Finnland I.J 1927 auf 8 % sämtlicher Todesfälle, hatten aber bis 1956 schon 44 % erreicht. Der Autor war der Ansicht, dass diese Steigerung in der Hauptsache auf Abänderungen der Nomenklatur beruhte. Aber auch Noro (128) hat auf eine Zunahme der Herzerkrankungen in Finnland hingewiesen. In Finnland erschien 1954 eine Arbeit über das Auftreten von Herzinfarkten von Linko (97) in der eine starke Zunahme der Fälle in der Innermediz. Abtlg der Universitätsklinik in Tur

die Berufe der Infarktpatienten der prozentualen Verteilung dieser Gruppen an der Bevölkerung entsprechen und kamen zu dem Schluss dass der Beruf ohne Einfluss auf das Auftreten der Herzinfarkte sei. Dieselbe Ansicht äusserte Rathe (141) *USA*. Das Problem der Prädisposition der Ärzte wurde von Levine und Hindle (94) *USA* erörtert. Diese Autoren zeigten dass der Einfluss von Faktoren, die eine bestimmte Krankheit verursachen, von ausserordentlicher ethnologischer Bedeutung bei derjenigen Berufsgruppe sein müsse die in Bezug auf diese Krankheit ein besonders frühes Sterbealter zeigt. Der Sterblichkeitsdurchschnitt von 2000 Ärzten lag bei 66,3 Jahren der Durchschnitt bei Todesfällen an Coronarinfarkt überhaupt lag bei zwei Versuchsreihen a) bei 66 0 und b) 65,8 J Der Durchschnitt aller an Coronarinfarkten verstorbenen Patienten lag ebenfalls bei 65,8 J Nach Ansicht dieser Autoren machte das Leben des Arztes das Auftreten von Coronarinfarkten nicht wahrscheinlicher diese Erkrankung sei somit bei Ärzten nicht besonders stark verbreitet. Auch Chambers (30) *USA* war der Ansicht, dass zwischen Beruf oder Milieu und Infarkt ein Zusammenhang nicht nachweisbar sei. Auch Master (114) *USA* war der Ansicht, dass Infarkte bei Ärzten nicht häufiger seien als bei anderen Personen. Brahme und Ahlberg (24) *Schweden* haben darauf hingewiesen, dass die Infarktanfälligkeit der Landbevölkerung geringer ist als die der Stadtbevölkerung, und dass die gehobeneren Stände eine grössere Anfälligkeit aufzuweisen scheinen. In einem Material über an Infarkt erkrankten Soldaten zwischen 18—39 J haben Yater u.a. (166) *USA* festgestellt dass 91 der Betroffenen ihren eigenen Angaben nach zur Mittelschicht gehörten während sich der Rest auf mittellose Familien verteilte Eine Kontrollgruppe erbrachte ein Verhältnis von 63 % 37 % Die Berufsgruppen waren die folgenden

Fabrik u. Schwerarbeiter	41 1 %
Büro- u. Geschäftsangestellte	17 6 %
Beamte	22,1 %
Fach- u. Vorarbeiter	10 5 %
Farmer	5,8 %
Hausangestellte	1,0 %
Angehörige der Sozialfürsorge	1 7 %
Studierende	0,2 %

Nach Ansicht des Verfassers bestand Tendenz zu Infarkt bei Personen mit leichter Arbeit wie z.B. Beamten, Vorarbeitern usf. Aufschlussreich ist der Beitrag von Ryle und Russel (150) *England*, der zeigt, dass die Mortalität bei Männern der höchsten sozialen Schicht (I) im Alter von 45—55 Jahren zehnmal so hoch wie bei der entspr Frauengruppe war und dass diese Männer einer besonders starken Verantwortung und "Stress" ausgesetzt waren. Wie die Autoren zeigten, geht die Infarktmortalität sowohl für Männer wie für Frauen mit dem Absinken des sozialen Standards merkbar zurück. Nach diesen Autoren waren Ärzte besonders stark betroffen.

Björck und Blomquist (12) *Schweden* haben mitgeteilt, dass die Sterb-

Zeitraum, aus dem die einzelnen Angaben stammen, muss auch die Standortfrage bzw das Aufnahmegebiet der betr Krankenhäuser in Betracht gezogen werden. In Landbezirken ist der Weg zum Krankenhaus oftmals lang und mühsam, die Patienten können vor der Aufnahme versterben. Gerade diese Fälle bleiben dann häufig undiagnostiziert. Auf diese Möglichkeit wird von Räsänen (151) hingewiesen. Diese Kliniken haben also relativ mehr solche Fälle die die kritischen ersten Tage hinter sich haben, so dass die Heilungsaussichten günstiger sind. Sind dagegen die Verkehrsverbindungen zum Krankenhaus gut, so kann der Patient fast sofort nach dem Anfall eingeliefert werden und dort im Verlauf der ersten kritischen Tage versterben.

Tabelle 1

Autor	Jahr	Mortalität in v.H.	Anzahl der Fälle
Conner und Holt (33)	1930	16,2	287
Björck u.a. (13)	1934	43	30
Master (106)	1935	10 7	75
Hochrein und Schneyer (74)	1936	71	226
Rosenbaum (147)	1941	44	208
Woods und Barnes (183)	1942	46,9	128
Brahme und Ahlberg (24)	1947	40,5	158
Mintz und Katz (119)	1947	23.6	572
Yater u.a. (Pat. unter 40 J) (186)	1948	52	866
Wright u.a. (keine antikoagul. Behandlung) (184)	1948	24	368
Wright u.a. (antikoagul. Behandlung) (184)	1948	14,4	432
Billings u.a. (11)	1949	40 4	240
Helander (69)	1949	30	193
Doscher und Poindexter (38)	1950	15,5	414
Wällgren (185)	1950	30	179
Eckerström (44)	1951	55	242
Newman (Pat. unter 35 J) (128)	1951	80	100
Russek u.a. (149)	1951	33,4	1047
Räsänen (151)	1951	22,9	180
Linden (95)	1952	45,5	544
Björck u.a. (13)	1953	37	143
Burstein (28)	1953	13,3	127

Familienstand

Die Verteilung auf Verheiratete und Ledige ist von den Forschern sel tener beachtet worden. Das Material von Bean (7) bestand grösstenteils aus strapazierten Personen, Arbeitern und Hausfrauen. 22 4 % des Gesamt materials von Master Dack und Jaffe (109) waren Hausfrauen. Von den 63 Frauen im Material von Brahme und Ahlberg (24) war nur eine einzige unverheiratet. Das Material von Ryle und Russell (150) verzeichnet 36 ver heiratete und 11 alleinstehende Frauen nur 5 der letztgenannten wa ren berufstätig Blörck u.a. (13) konnten keinen Unterschied zwischen Hausfrauen und berufstätigen Frauen eruieren. Die Herzinfarktmortalität war nach Lew (92) bei Verheirateten geringer als bei Ledigen Geschiedenen oder Verwitweten.

Zusammenfassend kann man fest stellen, dass der Anteil der verheirateten Frauen am Infarktmaterial ein zelner Publikationen auffallend hoch ist.

Erblichkeit

Der Erblichkeit wird beim Herzin farkt grosse Bedeutung beigemessen. Diese Auffassung vertraten schon 1929 Levine und Brown (93) Nach Rathe (141) waren in 48 % von 274 Infarktfällen hereditäre kardio-vaskuläre Erkrankungen aufgetreten. Cassidy (29) kommt auf eine kardiovaskuläre Heredität von 50 % Bei einer Untersuchung der kardio-vaskulären Heredität einer Gruppe jun ger Infarktpatienten konstatierten Yater u.a. (186) eine Heredität, die viermal höher lag als die einer Kontrollgruppe. Eine Arbeit von Billings u.a. (11) über 240 Infarktpatienten ergab hereditäre Herzerkrankungen bei 45 % der Fälle. Alvord (3) zeigt, dass die Disposition für Infarkte bei verschiedenen Familien abweichend ist. Newman (126) mass dem genetischen Faktor grösstes Gewicht bei zu demselben Ergebnis kam auch Roen (144) Wie Gertler (52) mit teilt, kommt Heredität auch bei den Eltern junger Infarktpatienten vor — hier waren die Zahl der Coronarer krankungen doppelt so hoch wie bei einer Kontrollgruppe. Scherf und Boyd (152) gaben eine hereditäre Disposition bei Coronarsklerose in 40 % an, und auch Shaffer und Chapman (158) betonten die Bedeutung der Heredität. Thomas und Cohen (168) haben das Auftreten von Coronarerkrankungen bei den Verwandten von 266 Medizinstudenten untersucht und konnten hierbei feststellen, dass Coronarerkrankungen bei Ver wandten von Personen mit solchen Erkrankungen viermal häufiger wa ren als sonst. Wie Bor (22) mitteilte, traten bei 70 % der Infarktpatienten hereditäre Belastungen mit Herz oder Kreislauferkrankungen in der Anamnese auf. Auch Gofman (56) betonte die Bedeutung der Heredität.

Zusammenfassend darf festgestellt werden dass frühere Forscher eine ziemlich deutliche hereditäre Dispo-

(176) Bean (7) Master Dack und Jaffe (113) Woods und Barnes (183) Levine und Hindle (94) Chambers (30) Mintz und Katz (119) Hellmuth (70) Brahme und Ahlberg (24) Wright u.a. (184) Billings u.a. (11) Doscher und Poindexter (38) Helander (69) Jervell und Eltinger (79) Wällgren (185) Räsänen (151) Blörck u.a. (13) Linko (97) und Ekvall (48)

Nach Linden (95) war das Durchschnittsalter bei Männern 64 bei Frauen 68 Jahre. Es dürfte vielleicht richtiger sein, das "Herzinfarktalter" durch Nennung der hauptsächlich betroffenen Altersgruppe nicht aber durch einen Durchschnittswert für das gesamte untersuchte Material anzugeben. Nach dieser Methode ergeben sich die meisten Fälle bei Conner und Holt (33) zwischen 56—60 J., bei Master Dack und Jaffe (111) 45—65 J., Doscher und Poindexter (38) 50—60 J., Eckerström (44) 61—70 J., Räsänen (151) 50—59 J., Shaffer und Chapman (158) 40—60 J., Ekvall (48) 60—69 J Westlund und Hougen (174) 70—74 Jahre. Wie Parker u.a. (134) zeigen sind 88 % der Coronarpatienten zwischen 50—80 Jahre alt. In einer Schrift von Russek u.a. (148) heisst es dass von 1047 Patienten 618 unter 429 über 60 Jahre alt waren. Järvinens Material (81) enthält nur Sterbefälle und verzeichnet die meisten im Alter von 60—69 Jahren.

In dem Material, das das Alter aller behandelter Herzinfarktpatienten mit dem Alter der Todesfälle vergleicht, wird festgestellt, dass das Durchschnittsalter der letzteren Gruppe höher ist, d.h. dass jüngere Patienten günstigere Aussichten haben. Levine und Brown (93) geben das Durchschnittsalter der Coronarpatienten mit 57 8 Jahren an, während Levine und Hindle (94) ein durchschnittliches Alter der an Coronarkrankheiten Verstorbenen mit 65,8 Jahren berechneten. Das Material von Woods und Barnes (183) gibt einen Gesamtdurchschnitt von 55 bei einem Durchschnitt von 51,3 für die Überlebenden und 59,2 für die Verstorbenen Diese Autoren hatten eine Verdoppelung der Infarkttodesfälle von Patienten über 60 Jahren errechnet. Brahme und Ahlberg (24) kommen auf ein männliches Durchschnittsalter der Infarktpatienten von 61 J., bei einem Durchschnittsalter der Verstorbenen von 62,7 J Die entsprechenden Zahlen bei weibl. Patienten sind 64 6 und 65 J Nach Yater u.a. (186) war die Mortalität bei Männern zwischen 35—39 J höher als bei Männern zw 20—24 J Das totale Durchschnittsalter der Männer wird von Wällgren (185) mit 60 das der verstorbenen mit 66 J angegeben, während die entspr Zahlen für Frauen bei 66,1 und 69,8 J liegen. Zu ähnlichen Resultaten sind auch Räsänen (151) Linden (95) Blörck u.a. (13) Ekvall (48) sowie Westlund und Hougen (174) gekommen. Helander (69) hat sein Material nach der Schwere der Fälle in drei Gruppen eingeteilt es ist hierbei erkennbar dass sowohl das Durchschnittsalter wie die Sterblichkeit mit der Schwere der Fälle fortschreitet. Russek u.a. (148) haben darauf hingewiesen dass die Mortalität nicht vom

reren Rückfällen als Infarkt behandelt wurden, werden jetzt erkannt die Rückfälle gelangen als solche in die Statistik.

Mintz und Katz (119) haben 572 Fälle publiziert, von denen 43 Rückfälle waren. Wright u.a. (184) haben den Rückfall Prozentsatz in zwei Materialen mit 24 % und 22 % angegeben. Wie Eckerström (44) mitteilt, hatten 11 von 242 Infarktfällen wenigstens einmal vorher einen leichteren Infarkt gehabt während Gofman u.a. (55) bei 359 Infarktpatienten 39 Rückfälle verzeichnen. Linden (95) äussert, dass frühere Infarkte die Prognose nicht beeinflussen, wenn der Rückfall nicht innerhalb weniger Monate eintrat. Blörck u.a. (13) berichten, dass von 143 Infarktfällen i.J. 1953 26 ihren zweiten Infarkt und 5 ihren dritten hatten gegenüber 8 bzw. 0 bei 30 Fällen i.J. 1934. Es ergab sich für das Jahr 1953 eine Mortalität von 6? % bei Rückfallinfarkt gegenüber 31 % für Patienten mit Erstinfarkt. Das Material von Gordin (57) das 1953 publiziert wurde, bringt einen Rückfallinfarktsatz von 17.1 %. Wie Blomquist u.a. (16) mitteilen, war das Rückfallsrisiko während des ersten Jahres grösser als später; die unmittelbare Mortalität bei Rückfällen gibt er als etwa genauso hoch wie bei Erstinfarkt an. Auch Bjerkelund (14) verzeichnet während des ersten Nachjahres eine erhöhte Rückfallsfrequenz.

Zusammenfassend ist festzustellen dass die Frequenz der Infarkt Rückfälle im Material der verschiedenen Autoren stark schwankt.

Hypertonie

Die Rolle der Hypertonie im Zusammenhang mit Herzinfarkten ist bisher noch nicht ganz geklärt. Die Mehrheit der Forscher ist einer Meinung in dem Punkte dass hoher Blutdruck oftmals mit Coronarleiden auftritt das prozentuale Auftreten von Hypertonie und Coronarleiden dagegen ist nach dem Material der einzelnen Autoren sehr schwankend. Das ist u.a. darin begründet was die betr. Autoren mit "hohem" Blutdruck meinen auch spielt natürlich die Zusammensetzung des jeweiligen Materials eine Rolle.

Das Material von Levine und Brown (93) zeigt bei 58 von 145 Coronarthrombose-Patienten Hypertonie besonders häufig war erhöhter Blutdruck bei jungen weiblichen Patienten. Das Material von Conner und Holt (33) verzeichnet in 34 % der Fälle frühere Hypertonie im Material von White und Bland (176) zeigt sich erhöhter Blutdruck in 50 von 200 Fällen. Die letzteren setzten als Grenze für erhöhten Blutdruck 160/110 mmHg an — diese Grenze benutzte auch Palmer (133) der in seinem Material 73 % Hypertoniefälle verzeichnet. Alle 20 weibl. Patienten hatten — mit einer Ausnahme — erhöhten Blutdruck. Glendy Levine und White (54) konstatierten in einem Coronarmaterial junger Infarktpatienten bei 16.6 % Hypertonie. 49,8 % der Coronarinfarktfälle im Material von Bean (7) hatten einen Blutdruck von mehr als 160/110. Master Dack und Jaffe (112) stellten

(183) Eckerström (44) Linden (95) Linko (97) Lee und Thomas (91)

Wird das Material in verschiedene Altersgruppen eingeteilt so ergeben sich andere Verhältnisse. Es ist nämlich zu erkennen, dass die Erkrankung bei den Frauen jüngerer Altersgruppen überaus selten ist, während die Unterschiede bei den älteren Jahr gängen weniger stark sind. Glendv Levine und White (54) haben dargelegt, dass Coronarerkrankungen bei Personen unter 40 Jahren im Verhält nis 24 1 (Männer Frauen) auftreten, was also das Sechsfache der nicht nach Altersgruppen gegliederten Normalwerte ist. Nach Woods und Barnes (183) tritt die Coronarocclusion bei Männern meist vor Errei chung des 60 Lebensjahres auf, während sie bei Frauen erst nach dem 60 Jahr häufiger auftritt. Wie Cassidy (29) angibt, sind 58 % der betroffenen Frauen, aber 48 % der Män ner über 60 Jahre alt. Nach Mintz und Katz (119) waren 75 % der Frauen, 62,5 % der Männer zwischen 50—70 Jahre alt. Hellmuth (70) verzeichnet eine sechsfache Frequenz von Männern unter 40 Jahren gegenüber Frauen unter 40 J Aus einer Tabelle, die Ryle und Russell (150) über Todesfälle bei Coronarinfarkten aufgestellt haben, geht hervor dass die Häufigkeit bei Männern bis zum Alter von 55 Jahren das Fünffache beträgt. Hiernach findet nach und nach eine Angleichung statt in der Altersgruppe über 75 J ist das Verhältnis 1,8 1 Dieselbe Tendenz zeigt sich im Material von Eckerström (44) und zwar wird sie hier nach dem 65 Lebensjahr noch stärker und führt sogar zu einem weiblichen Übergewicht. Ähnliche Ergebnisse ergaben die Untersuchungen von Räsänen (151) Ekvall (48) Peel (136) Järvi nen (81) sowie von Ikkala und Kai painen (75) Keys (85) weist darauf hin, dass Männer der Erkrankung zunächst mehr ausgesetzt sind, dass die Frauen jedoch mit fortschreitendem Alter ihre günstige Stellung einbüssen. Die relative Immunität der Frauen scheint mit ihrer Fertilitätsperiode parallel zu gehen. Keys hat a.a.O (87) festgestellt dass das Geschlecht nicht als Basis für den Herz infarkt anzusehen ist nachdem Frauen in Nordeuropa anfälliger sind als Männer in Südeuropa — der Autor stellt hierzu die Frage ob man etwa die südeuropäischen Männer für weniger männlich halten müsse. Lee und Thomas (91) weisen darauf hin, dass der Scheitel der Kurve bei Frauen später liegt als bei Männern, so auch Hilleboe (72) Zwei Spezial untersuchungen, Newman (126) und Gertler u.a. (53) befassen sich nur mit jungen Patienten und erweisen hier eine ausserordentliche Dominanz der Männer Das Material von Newman (126) umfasst 100 Patienten zwischen 21 und 35 Jahren, davon 99 Männer und eine Frau. Die Patienten von Gertler (53) waren zwischen 23 und 40 Jahren, es waren 97 Männer und 3 Frauen. Die von Ikkala und Kalpainen (75) eruierten Ergebnisse weisen in dieselbe Richtung.

Zusammenfassend darf man sagen, dass die Angaben über die Mortalität bei den einzelnen Autoren ein sehr

angesetzt, während Doyle u.a. (40) die Grenze bei einer Populationsuntersuchung auf 150/100 ansetzten.

Zusammenfassend lässt sich feststellen, dass die meisten Autoren bei den Coronarinfarktpatienten eine ziemliche Verbreitung von Hypertonie festgestellt haben, u.s.w mit einem höheren Prozentsatz für Frauen als für Männer Über die Bedeutung der Hypertonie für die Mortalität sind die Meinungen schwankend.

Tabak und Alkohol

Häufig fordern praktizierende Ärzte ihre Herzpatienten auf, das Rauchen einzustellen. Diese Einstellung gegenüber dem Rauchen findet Unterstützung durch die Auffassung der meisten Forscher die auf diesem Gebiet gearbeitet haben.

So z.B weist Gofman (56) in "Coronary Heart Disease" auf die Erhöhung des Risikos durch das Zigarettenrauchen hin. Hammond und Horn (65) haben in einem grossen Material Zusammenhänge zwischen der Herzinfarkt Mortalität und dem Tabakgenuss konstatiert und Hegglin (68) äussert die Meinung, dass das Rauchen die Coronarsklerose beschleunigt. Welcker (172) weist auf den plötzlichen Herztod junger Gewohnheitsraucher hin und erwähnt das gleichzeitige Auftreten lipoider Verdickungen der Coronargefässe Wilson und Johnston (179) äussern, dass das Rauchen bei Coronarpatienten zu Coronarspasmen und zu Angina pectoris führen kann. Die gleiche Ansicht vertritt Nylin (129) Nach Sprague (161) müssten Angina-pectoris-Patienten das Rauchen einstellen. Demgegenüber hat v Ahn (1) darauf hingewiesen, dass Angina pectoris als Folge von Tabakgenuss selten ist nach Scherf und Boyd (152) wiederum ist die Bedeutung des Nikotins für die Aetiologie der Coronarsklerose unsicher

White und Sharber (177) vertreten die Auffassung dass der Tabak für die Entstehung von Coronarleiden keine entscheidende Rolle spielt und dieser Ansicht sind auch Master Dack und Jaffe (109) Cassidy (29) erwähnt, dass ihm kein Fall von Heilung der Angina pectoris durch das Einstellen des Rauchens bekannt geworden sei.

Das Material von White und Sharber (177) verzeichnet 46 1 % Nichtraucher und 24 4 % Gewohnheitsraucher Die entsprechenden Zahlen für das Material von Blumer (17) waren 34 % zu 30 % bei Bean (7) 33 % zu 28 % im Material von Cassidy (29) 17 6 % zu 39,8 % In einer Arbeit von Glendy u.a. (54) über Personen unter 40 Jahren war der Prozentsatz der Raucher 93 v.H., was die Autoren für mehr als normal hielten. Auch Gertler u.a. (53) konstatieren, dass die Coronarpatienten stärkere Raucher sind. Einen Satz von 50 % leichten Rauchern verzeichnet das Material von Jakobs (76) 68 % der 19—39 jährigen Soldaten in Yaters Material (166) rauchten mehr als 10 Zigaretten pro Tag, während sich für eine Kontrollgruppe 19 % ergab. Wie Ralli und Oppenheimer (140)

Gertler u.a. (53) traten Herzinfarkte meist während der Herbst und Wintermonate auf. Nach der Arbeit von Blörck u.a. (13) sind die Fälle ziemlich gleich über das Jahr verteilt kleine Steigerungen für Juli und Dezember fallen statistisch kaum ins Gewicht. Das Material von Ekvall (48) ergibt für das Auftreten von Herzinfarkt innerhalb der verschiedenen Jahreszeiten folgendes Bild

I	Quartal (Dez.—Feb.)	55 Fälle
II	Quartal (März—Mai)	60 Fälle
III.	Quartal (Juni—Aug.)	49 Fälle
IV	Quartal (Sept.—Nov.)	68 Fälle

also für das Winterhalbjahr (Okt.—März) 113 für das Sommerhalbjahr (April—Sept.) 119 Fälle. Da die Winter Nordschwedens kalt sind, hebt der Autor hervor dass die Kälte das Auftreten von Infarkten nicht beeinflusst hat. Im Material der Autoren Schnur (155) Dotzauer und Naeve (39) sowie Jensen (77) treten die meisten Infarktfälle während des Winters auf, während sich bei Pell und D Alonzo (137) die Fälle im Sommer häufen. Jensen gibt ausserdem eine Spitze im Mai an.

Die Tageszeit, zu der der Infarkt einsetzt, ist ausserdem u.a. von Bean (7) beobachtet worden. Von 59 untersuchten Fällen trat der Infarkt bei 28 am Morgen, bei 1 am Nachmittag bei 27 am Abend und bei 3 während der Nacht auf. Nach Mitteilung von Master u.a. (109 111 116) hatte die Tageszeit keine Bedeutung für das Auftreten des Infarkts. Die Anfälle verteilten sich in diesem Material auf die folgenden Tageszeiten (in v.H.)

07—13	Uhr	28,9
13—19	Uhr	23,1 %
19—01	Uhr	22,5 %
01—07	Uhr	25,5 %

Nach Ejrup und Nylin (47) traten die meisten Infarktfälle bei Nacht auf. Nach Gertler u.a. (53) setzte der Anfall bei 62 % der Fälle zwischen 07^{30} und 19^{00} Uhr ein. Das Material von Ekvall (48) zeigt das Auftreten der Anfälle bei 17,2 % der Patienten zur Nachtzeit.

Der Aktivität die dem Infarktanfall vorausgegangen ist, haben mehrere Forscher ihr Interesse gewidmet. Da jedoch eine zuverlässige Statistik über diese Aktivität eine in casu geführte eingehende Anamnese erfordert, haben sich viele Autoren damit begnügt zu konstatieren dass der Mensch seinen Beschäftigungen im allgemeinen bei Tage nachgeht und diese Aktivität deshalb die normale genannt. Abends hält der Mensch Ruhe, nachts schläft er. Bei einem Material dieser Art wird das Auftreten des Infarkts meistenteils mit der normalen Aktivitätszeit zusammenfallen. Andere Autoren haben sich um eine Gliederung der Aktivität in geistige und körperliche bemüht. White (175) teilt mit dass Patienten mit Angina pectoris sich vor Eile, Sorgen, Überanstrengung kaltem Wetter und zu starkem Essen hüten müssen. Eine Winterreise in den Süden kann wie er meint, das Leben verlängern. Luten (100) führt zwei Fälle an, in denen der Anfall unmittelbar nach dem

patienten 33 Abstinente bei 109 Nicht Abstinenten bei den Frauen bezeichneten sich 61 als abstinent 3 genossen regelmässig Alkohol.

Zusammenfassend kann festgestellt werden, dass eine ätiologische Bedeutung des Tabakgenusses als Faktor für Coronarinfarkte nicht erwiesen werden konnte doch haben einige Forscher nachgewiesen, dass Tabakgenuss in bestimmten Fällen Anfälle von Angina Pectoris auslösen konnte. Es sind also Arbeiten publiziert worden in denen ein statistischer Zusammenhang zwischen Herzinfarktmortalität und Tabakgenuss belegt wurde. Dagegen waren die Forscher der Ansicht, dass Alkoholgenuss keine ätiologische Wirkung hat, sondern dass dem Alkohol bei stenokardischen Beschwerden sogar eine subjektiv wohltuende Wirkung zukommen kann.

Diätfragen

Die Bedeutung der Ernährung hinsichtlich Entstehung von Coronarsklerose und Arteriosklerose im allgemeinen ist während der letzten Jahre zu einer immer aktuelleren Frage geworden. Neu ist das Problem allerdings nicht — bereits 1934 haben Master u.a. (105) mitgeteilt dass zur Heilung von Coronarthrombosepatienten schon sieben Jahre lang mit glänzendem Erfolg eine Diät von 800 Kalorien per Tag angewendet wurde. Dieselben teilten 1936 mit (107) dass durch den niedrigen Kaloriensatz der Basalmetabolismus herabgesetzt werde was zu langsamerem Puls Senkung des Blutdrucks und verminderter Arbeit für das Herz führe. Nach Ansicht dieser Autoren war eine derartige Diät oftmals geeignet Herzleiden zu beseitigen. Will man Klarheit über die ätiologische Bedeutung der Diät bei der Entstehung von Herzinfarkten gewinnen, dann dürfte es günstig sein, das vorhandene Material in zwei Gruppen zu gliedern. Eine Reihe der unten herangezogenen Autoren zeigt in ihren Untersuchungen dass die Herzinfarktfrequenz einer Bevölkerungsgruppe oder eines ganzen Volkes nachliess in Zeiten, während der die Bevölkerung Not litt und hungerte Eine andere Gruppe von Autoren hat Bevölkerungsgruppen miteinander verglichen, in deren Lebensbedingungen und Ernährung Unterschiede auftreten und hat hierbei Unterschiede in der Herzinfarktfrequenz der einzelnen Gruppen gefunden.

Von besonderer Aktualität ist zur Zeit die Cholesterolfrage doch scheint deren Behandlung im Zusammenhang mit vorliegender Untersuchung, die sich ja in erster Linie mit sozial medizinischen Faktoren befasst, nur in beschränkterem Umfang möglich. Es sei hier immerhin die Untersuchung von Dawbers u.a. (34) erwähnt. In dieser Populationsuntersuchung für Framingham die 4469 Personen erfasst, konnten die Autoren feststellen, dass sich bei 12 % derjenigen Personen, die vier Jahre lang Serumcholesterolwerte von über 260 mg % hatten, Coronarerkrankungssymptome zeigten. Auch Doyle u.a. (40) konstatierten in einer Popu

69 beim Auftreten des Infarktes gerade gearbeitet und sich dabei psychischer oder physischer Anstrengung ausgesetzt. Järvinen (81) hat die Bedeutung von "Stress" hervorgehoben und 6 Sterbefälle während der Visite in Krankenhäusern beschrieben. Halonen (63 64) hat betont, dass auch stenokardischer Schmerz nach Mahlzeiten und gelegentlich während einer Ruhepause auftreten kann, dass er aber vor allem eine Anstrengung ist, die den Schmerz direkt hervorruft. Bei einem Teil der Patienten kann der stenokardische Schmerz auch von Gemütsbewegungen herrühren.

Zusammenfassend darf man feststellen, dass einige Autoren im Hinblick auf jahreszeitliche Schwankungen der Infarktfälle ein gewisses Übergewicht für den Winter angeben, während andere das Auftreten derartiger Tendenzen nicht haben konstatieren können. Was die Tageszeit betrifft, so haben einige Autoren eine starke Frequenz zur Nachtzeit eruiert während andere wiederum keine bevorzugte Tageszeit feststellen konnten. Hinsichtlich der Bedeutung von Anstrengungen sind die Meinungen über die Auswirkungen von physischem bzw psychischem Stress geteilt.

Soziale Schichtung

Es hat vor allem früher die Auffassung geherrscht, dass besonders die vermögenden Schichten von Herzinfarkten heimgesucht würden. So wurde dieses Leiden mancherorts "Wall-Street Krankheit" genannt weil es angeblich besonders unter den in ständiger Hetze lebenden Geschäftsleuten und auch unter Ärzten verbreitet sei. Diese Ansicht äussert auch Smith (160) *USA* der nachweist, dass das Auftreten von Coronarsklerose bei Ärzten bedeutend häufiger war als bei anderen Berufsgruppen.[1] In der Arbeit von Bean (7) *USA* wurden vor allem strapazierte Personen Arbeiter und Hausfrauen herangezogen. Nach einer von Master u.a. (109) *USA* herausgegebenen Tabelle über Coronarthrombosefälle verzeichnete das Material die folgenden Berufsgruppen

Arbeiter	37,5 %
Geschäftsangestellte	5 %
Büroangestellte	10 %
Geschäftsleute	10 %
Freiberufl. Tätige	7,8 %
Hausfrauen	22,4 %
Pensionäre sowie Berufslose	7,3 %

Eine Arbeit von Glendy u.a. (54) *USA* zeigt, dass die Patienten dieses Materials (Personen unter 40 Jahren) zumeist junge Geschäftsleute waren. Die meisten Personen eines Kontroll Materials von Patienten im Alter von 80 J und mehr wohnten auf *dem Lande oder in Kleinstädten und* gehörten der Mittelklasse an. In einer weiteren Publikation von Master u.a. (111) *USA* zeigen die Autoren, dass

[1]) Ausser dem Literaturhinweis wird das Land, auf das sich die betr Publikation bezieht, angegeben, weil die sozial Struktur der einzelnen Länder z.T ausserordentlich unterschiedlich ist.

1941—1944 konstatierte starke Rückgang dürfte wohl kaum darauf beruhen, dass die Ärzte zu einen selteneren Gebrauch dieser Diagnose übergegangen waren, sondern dass diese Erkrankung während besagter Zeit tatsächlich seltener war. Das auf das Jahr 1947 fallende Maximum des neuen Ansteigens deutete der Autor so, dass eine Reihe von Arteriosklerotikern, deren Leben durch kriegsbedingte Milieuveränderungen verlängert worden war, nunmehr ihrem Leiden erlagen. Malmros (103) hat dargelegt, dass die Mortalitätsverminderung an Arterio- und Kardiosklerose während des Krieges vorwiegend bei der Stadtbevölkerung ins Auge fiel, da diese kaum Möglichkeiten hatte, sich über die Rationen hinaus etwas Essbares zu verschaffen. Wie zwei von Ström und Jensen (164) publizierte Kurven über die Mortalität der Blutkreislauferkrankungen und den Fettverbrauch während der Jahre 1938—1948 zeigen, ging der Fettverbrauch während des Krieges zurück und stieg anschliessend wieder an — die Mortalitätskurve zeigt genau dieselbe Veränderung. Nach Ström und Rygh (165) ging während des Krieges die Sterblichkeit an kardiovaskulären Krankheiten in England, Schweden, Dänemark und Norwegen zurück. Wie Berg (10) unterstreicht, zeigte das klinische Bild von Kreislaufstörungen während Hungersnöten in Deutschland einen ganz andersartigen Verlauf als bei normaler Versorgungslage. Nach Neth und Schwarting (125) zeigte die Coronarsklerose bei Obduktionen während der Jahre 1945—1953, als die Versorgungslage zunächst sehr schlecht und dann allmählich besser geworden war, die gleichen Tendenzen, doch hatten die Herzinfarktfälle zugenommen. Die Autoren hielten die Coronarsklerose nur für *einen* Faktor der Pathogenese des Herzinfarkts, der auslösende Faktor hatte nach ihrer Ansicht während der Hungerjahre gefehlt. Im Jahre 1956 äusserte man seitens des amtl. finnischen Ernährungskomités, dass der Anteil der Fettstoffe an der Ernährung von rd. 25 % während der 30-er Jahre auf rd. 35 % gestiegen war; infolge davon seien Verfettung und Erkrankungen der Kreislauforgane und des Herzens bei der Bevölkerung aufgetreten. Pierach (139) hat darauf hingewiesen, dass Myokardinfarkte während der Hungerjahre in Deutschland während u. nach dem zweiten Weltkrieg eine Seltenheit waren. Schettler (153) zeigt, dass die Kurven der Sklerosesterblichkeit während der Jahre 1938—1953 in der Tat etwa parallel mit den Kurven für den Fettverbrauch dieser Jahre verlaufen.

Kuczynski (90) beobachtete, wie 1925 mitgeteilt, eine starke Verbreitung von Arteriosklerose bei den Kirgisen, deren Kost fast ausschliesslich aus Fleisch besteht. Nach dem Autor ist für dieses Volk reichlicher Alkoholgenuss und Arbeitsunwilligkeit kennzeichnend, also Faktoren, die zu der starken Verfettung dieser Menschen beigetragen haben dürften. Ehrström (45) hat eine ähnliche Untersuchung bei den grönländischen Eskimos durchgeführt; diese Arbeit

lichkeit an Kardiovasculärkrankheiten bei der Stadtbevölkerung weitaus höher lag als bei der Landbevölkerung. Scherf und Boyd (152) *Österreich* waren der Meinung, dass der Beruf beim Auftreten von Coronarsklerose keine Rolle spielt. Jacobs (76) *USA* vertrat dieselbe Auffassung. Ein Material von 100 jungen Infarktpatienten (21—35 J.) der Armee hat Newman (126) *England* veröffentlicht, 9 der Betroffenen waren Offiziere, höhere Ränge als Leutnant traten nicht auf. Die meisten waren Angehörige der Sozialklassen IV u. V (nach Regist. General). Nach Ansicht des Autors war ein Zusammenhang zwischen leichter Verantwortung und "Stress" und dem Auftreten von Infarkt nicht nachweisbar. Gertler u.a. (53) *USA* haben in einer Publikation über Patienten unter 40 J. nicht direkt ausgesprochen, dass bei Intellektuellen Prädisponiertheit besteht, weisen aber auf ein Vorwiegen bestimmter Berufsgruppen in den betr. Serien hin. In einer Publikation über Angestellte der Londoner Verkehrsgesellschaft und anderer öffentlicher Einrichtungen zeigten Morris u.a. (121) *England*, dass Männer mittleren Alters, die hauptsächlich körperliche Arbeit verrichten, weniger infarktanfällig sind als Angestellte mit intellektueller Tätigkeit. Dasselbe Resultat haben auch Biörck u.a. (13) *Schweden* erhalten, als sie die prozentuale Verteilung von Infarkten bei Arbeitern und Intellektuellen untersuchten. Das Material von Ekvall (46) *Schweden* erfasst hauptsächlich die Landbevölkerung und es ergab sich eine geringere Herzinfarktfrequenz gegenüber bestimmten anderen Orten. Der Autor wies darauf hin, dass die Landbevölkerung weniger dem "Stress" ausgesetzt sei und dass sie mehr körperliche Arbeit verrichte. Im Berufsverzeichnis der Arbeit von Westlund und Hougen (174) *Norwegen* über männl. Pat. unter 70 J. treten verhältnismässig mehr Beamte und wesentlich weniger Arbeiter auf als was man in Anbetracht des Anteils dieser Gruppen an der norwegischen Stadtbevölkerung annehmen könnte. Bronte-Stewart u.a. (25) *Süd Afrika* unterstreichen, dass Coronarerkrankungen bei Weissen in Süd Afrika viel häufiger auftreten als bei Farbigen, und dass solche bei Bantus äusserst selten sind; das soziale Gefälle zeigt dieselbe Richtung. In diesem Zusammenhang wurden von den Autoren auch diätetische Fragen berührt, auf die weiter unten einzugehen ist. Nach Lee und Thomas (91) *USA* hat der "sozialökonomische" Faktor keinerlei Bedeutung. Morris und Crawford (122) *England* haben darauf hingewiesen, dass Berufe, die körperliche Anstrengung erfordern, Männer vor ischämischer myokardialer Fibrose schützen.

Zusammenfassend darf man sagen, dass eine einheitliche Meinung der verschiedenen Forscher über die Bedeutung von Beruf und sozialer Stellung beim Auftreten von Herzinfarkten nicht besteht. Diejenigen Arbeiten, die einen Vergleich zwischen Land- und Stadtbevölkerung ziehen, konstatieren eine höhere Frequenz bei der Stadtbevölkerung.

1939 die Arteriosklerose-Sterblichkeit Italiens weit unter der Schwedens lag. Wie Dock (37) äussert war Arteriosklerose bei der Arbeiterbevölkerung von China Indonesien, Afrika und Zentralamerika selten. Das beruhe auf Besonderheiten der Ernährung nicht aber auf der Rasse da in der US-Army Coronarerkrankungen auch bei Negern und bei Indianern vorkamen. Keys (85) hat betont, dass Coronarerkrankungen hauptsächlich in denjenigen Gebieten auftreten, in denen animalische Nahrung verzehrt wird. Morris u.a. (121) massen der Sozialgruppe und hiermit zusammen hängenden Ernährungsfragen Gewicht bei. Bronte-Stewart u.a. (25) publizierten eine Untersuchung die die Ernährung und das Einkommensniveau der Weissen Farbigen und der Bantus in Kapstadt beobachtet Es zeigt sich, dass die Weissen doppelt so viel Fett verzehren wie die Bantus, während sich für die übrigen Farbigen Mittelwerte ergaben. Sowohl der Fettgehalt der Ernährung wie der Serumcholesterolspiegel stiegen im Verhältnis mit dem Einkommen. Nach Vogelpoel und Schrire (181) waren in Kapstadt bei Bantus EKG-mässig erfasste Infarkte äusserst selten, gewöhnlicher bei den anderen Farbigen *und am häufigsten bei den Weissen.* Wie Keys u.a. (86) zeigten, bildeten die Fette 35 % der Kalorienwerte bei der Ernährung der Weissen von Kapstadt (Bantus 16 % andere Farbige 25 %) Nach Gordon (59) treten Coronarerkrankungen in England meist in den blühenden und "better fed Gegenden auf. Morrison (123) hat einen Bericht über eine Untersuchung veröffentlicht während der er Patienten mit Coronarsklerose 12 Jahre lang beobachtete. 50 der Patienten nahmen eine Diät mit niedrigen Fett und Cholesterolsätzen zu sich die anderen verzehrten normale (amerikanische) Kost. Nach Verstreichen der 12 Jahre war kein Patient der zweiten Gruppe mehr am Leben, von ersterer 38 % Nach dem Autor liesse sich hieraus der Schluss ziehen, dass eine an animalischen Stoffen reiche Kost die Coronarsklerose begünstigt.

Roine u.a. (145) haben die Kost der Bevölkerung von Ost und Westfinnland verglichen, da in Ostfinnland kardiovaskuläre Erkrankungen häufiger auftreten. Bezüglich der Fettkost konnten Unterschiede nicht festgestellt werden doch zeigte es sich, dass die Nahrung in Westfinnland mehr Jod, Ascorbinsäure und E-Vitamin enthielt. Rauterberg (142) hat ein Ansteigen der Infarktfälle in Berlin für die Zeit 1945—1954 nachgewiesen und eine gleichzeitige Erhöhung des Fettkonsums festgestellt. Nach Morris (120) und Schweitzer (156) beruhte die erhöhte Coronarsklerose-Frequenz auf Ernährungsfaktoren Scherf und Boyd (152) schreiben, dass *fettreiche Kost die* Entstehung der Arteriosklerose begünstige In diesem Sinne haben sich u.a. auch Borgström (23) und Keys (85) ausgesprochen. An obduziertem Material haben Vartiainen und Kanerva (171) nachgewiesen, dass Arteriosklerose während der Kriegsjahre als die Versorgungslage Finnlands

sition für Coronarerkrankungen nachgewiesen haben.

Frühere Stenokardie

Der Krankheitsverlauf des Herzinfarkts ist oftmals sehr dramatisch beschrieben worden wie ein Blitz aus heiterem Himmel" Dass der "Himmel" indessen durchaus nicht "klar" war haben die meisten Autoren gezeigt. So beschreibt Master u.a. (113) dass 59 % der 202 Patienten eines Materials auch früher schon anginöse Beschwerden hatten. Rathe (141) kam auf einen Satz von 37 % Mintz und Katz (119) zeigten dass 72,9 % eines Materials von insgesamt 572 Herzinfarktfällen schon vorher an Angina pectoris gelitten hatten. Nach Chambers (30) hatten Infarktpatienten, deren Anamnese Herzbeschwerden zeigte eine schlechtere Prognose 1947 betonte er dass mehr als die Hälfte derjenigen Infarktpatienten, die an Hypertonie litten, auch früher anginöse Beschwerden gehabt hatten. 49 4 % der Infarktpatienten in der Arbeit von Yater u.a. (186) hatten schon früher an anginösen Beschwerden gelitten. Nach Billings u.a. (11) war Angina pectoris in 54 % der Fälle früher aufgetreten und ergab — bei dieser Gruppe — eine Mortalität von 40 % während die Mortalität des Gesamtmaterials bei 40 4 % lag. Nach Angabe von Doscher und Poindexter (38) hatten 33,3 % anginöse Beschwerden gehabt, während Jacobs (76) auf 39,8 % kommt Gertler u.a. (53) errechneten 41 % Räsänens Material (151) zeigt frühere Stenokardie bei 61 7 % der Infarktpatienten. Die Mortalität bei Infarktpatienten die früher an Angina pectoris gelitten hatten zeigte gegenüber anderen ungefähr die gleichen Ausmasse. Ein entgegengesetztes Resultat ergibt sich bei Eckerström (44) wonach Infarktpatienten mit früherer Stenokardie eine höhere Mortalität aufweisen. In seinem Material — 242 Infarktpatienten - waren bei 37,2 % früher keine anginösen Beschwerden aufgetreten. Ähnlich sind die Resultate Lindens (95) der feststellt dass die Mortalität von Infarktpatienten ohne frühere Herzleiden 27 % bei früheren Beschwerden 55 % und bei schweren Beschwerden 73 % erreichte. Von den 232 Fällen im Material von Ekvall (48) hatten 65 1 % früher Herzbeschwerden gehabt, 42,2 % Angina pectoris.

Zusammenfassend kann man feststellen, dass nach Angabe der Autoren ein beträchtlicher Teil der Patienten schon früher anginöse Beschwerden gehabt hatte. Die Zahlenangaben über das Mortalitätsverhältnis zwischen Infarktpatienten mit bzw ohne frühere Angina pectoris schwanken.

Infarktrückfälle

Auf Grund der verbesserten Therapie darf man annehmen, dass die Anzahl der Rückfälle gestiegen ist. Leichtere Infarktfälle, die früher nicht erkannt und erstmals bei schwe-

III FRAGESTELLUNG

Wie das überblickte Schrifttum zeigt, war die Frequenz des Herzinfarkts nach dem zweiten Weltkrieg in verschiedenen Teilen der Welt steigend. Die Ursache für dieses Phänomen konnte nicht mit Sicherheit klargestellt werden, die verschiedenen Autoren haben verschiedene Theorien über den Frequenzanstieg geäussert.

Nach den Statistiken über die innermedizinischen Abteilungen des Maria-Krankenhauses zu Helsinki war auch hier ein Frequenzanstieg der Herzinfarktfälle zu verzeichnen, und es wurde für aufschlussreich gehalten zu untersuchen, ob diese Erhöhung eine faktische ist, oder ob sie nur scheinbar ist und auf Faktoren wie z.B. der Bevölkerungszunahme oder Veränderungen der diagnostischen Methode zurückgeht. Nachdem nun sowohl in Bezug auf die Diagnostik wie auf die Behandlung der Erkrankung während der Zeit 1945—1952 keine nennenswerten Veranderungen aufgetreten sind, und nachdem i.J. 1952 die Antikoagulantiabehandlung und von 1953 an die unipolare EKG-Methode üblich wurde, wurde der Zeitraum 1945—1952 als Beobachtungszeit gewählt.[1]) Diese Zeit liess sich sodann noch einmal untergliedern in die Perioden 1945—1948 und 1949—1952, zwischen denen Vergleiche angestellt werden konnten. Es ist m.E. von nicht unerheblicher Bedeutung, diese 4-Jahresperioden zu vergleichen, da während dieser Zeit, wie schon erwähnt, Diagnostik und Behandlung im Maria-Krankenhaus ziemlich konstant waren, wogegen während dieser Zeit jedoch in Bezug auf die Versorgungslage und den allgemeinen Lebenstandard in Helsinki stärkste Veränderungen eintraten. Während die erste Periode durch Lebensmittelrationierung und eine äusserst angespannte allgemeine Versogungslage mit schnell fortschreitender Inflation charakterisiert ist, trat mit Aufhören der Lebensmittelbewirtschaftung im Herbst 1948 eine ausserordentlich schnelle Veränderung der Situation ein, und man darf behaupten, dass die schweren Nachkriegsjahre bei Beginn der zweiten Vierjahresperiode schon so gut wie überwunden waren.

Zweck dieser Untersuchung war es in erster Linie, Klarheit darüber zu erlangen, inwieweit bestimmte medizinische und soziale Faktoren an der Frequenzerhöhung Anteil haben. Deshalb wurden untersucht die Kor

1) W[illegible] der Krieg für Finnland [illegible] 1944 zu End

bei 56,5 % der männl. und bei 80 % der weibl. Infarktpatienten Hypertonie fest. Nach Gross und Engelberg (62) konnte bei 90 von 100 Herzinfarktpatienten nach Auftreten des Infarkts u. Abklingen der Initialattacke durch Kontrolle Hypertonie erwiesen werden. Während Bland und White (15) bei 41 % der Herzinfarktfälle erhöhten Blutdruck beobachten konnten, gaben Master, Dack und Jaffe (113) später einen Satz von 60,4 % an. Rathe (141) hatte eine Grenze von 140/90 mmHg angesetzt und war hierbei auf den Satz 63 % gekommen. Chambers (30, 31) teilte mit, dass 74 % der Patienten seines Materials erhöhten Blutdruck hatten. Ein sicherer Zusammenhang zwischen früher aufgetretener Hypertonie und Infarktmortalität liess sich nicht eruieren. In 27,1 % der Fälle von Cassidys Material (29) lag ein Blutdruck von mehr als 200/120 mmHg vor sowie in 70 % bei mehr als 160/100 mmHg. Mintz und Katz (119) gaben als Hypertensionsgrenze 90 mmHg diastolischen Druck an und gelangten nach dieser Festsetzung auf 29,7 % bei männl. und 49,4 % bei weibl. Patienten. Die Mortalität war bei den Männern 16,8 % bei den Frauen 30,8 %. Yater u.a. (186) haben in einem Material von 866 Männern im Alter 18—39 J. bei 14 % der Patienten durch Anamnese Hypertonie festgestellt — gegenüber 3 % einer Kontrollgruppe. Die Grenze war von diesem Autor auf 160/105 mmHg festgesetzt worden. Im Material von Billings u.a. (11) war eine Hypertonsionsgrenze von 150/100 mmHg angesetzt worden, wodurch sich ein Satz von 54 % ergab die Mortalität dieser Gruppe belief sich auf 37 % gegenüber 41 % bei Nicht-Hypertonikern. Helander (69) äusserte, dass der Blutdruck für die Mortalität bedeutungslos sei, zur selben Auffassung gelangten auch Master u.a. (115). Vom Material Doschers und Poindexters (38) waren 36 % Hypertoniker, während Jacobs (76) auf 34 % kam. Eckerström setzte eine Hypertoniegrenze von 160/110 mmHg an und kam auf 31 %. Räsänen (151) kam auf 32,5 % Hypertonie bei Männern und 54 % bei Frauen bei einer Grenze von 150/110 mmHg. In den Fällen von mässig erhöhtem Blutdruck (150—210 mmHg syst. Druck) ergab sich eine geringere Mortalität. Scherf und Boyd (152) waren der Meinung, dass in mehr als 50 % der Fälle bei Coronarsklerose und Thrombose Hypertonie vorlag. Hinsichtlich der Mortalität äusserte Linden (95) indessen keinen Einfluss der Hypertonie. Ekvall (48) hatte eine Hypertoniegrenze von 160/100 mmHg angesetzt und kam bei seinem Material auf 51,5 % bei männl. und 88,7 % weibl. Patienten. Die Hypertoniker hatten eine niedrigere Mortalität. Westlund und Hougen (174) kamen zum entgegengesetzten Ergebnis. Chapman u.a. (32) sowie Dawber u.a. (34) sahen in erhöhtem Blutdruck ein erhöhtes Risiko für Coronarleiden. Pell und D'Alonzo (137) waren der Ansicht, dass Hypertonie auf das Entstehen von Herzinfarkten, nicht aber auf die Prognose von Einfluss war. Die Grenze für erhöhten Blutdruck wird von der WHO auf 160/95 mmHg

IV MATERIAL

Bei dem Material handelt es sich um 569 Herzinfarktfälle die im Verlauf der Jahre 1945—1952 auf den innermedizinischen Abteilungen des Maria-Krankenhauses zu Helsinki gepflegt wurden. Es waren hiervon 88 Rückfälle u. zw 73 erste Rückfälle 14 zweite Rückfälle sowie 1 dritter Rückfall. 15 der Rückfallpatienten hatten ihren ersten Infarkt vor dem Jahr 1945 erlitten.

Die Diagnose stützt sich auf das klinische Bild sowie auf Labor- und EKG-Untersuchungen. Nahezu sämtliche Fälle die zum Exitus führten wurden obduziert. Die in dieser Untersuchung verarbeiteten Angaben fussen auf den Krankenberichten der Patienten, welche falls unvollständig im Rahmen der Möglichkeiten ergänzt wurden. So stammen Angaben über Beruf und Familienstand der Patienten z.T aus behördlichen Auskünften.

Wer die amtliche Statistik des Maria Krankenhauses durchsieht, wird für die Beobachtungszeit auf 654 Infarktfälle anstatt der hier verzeichneten 569 stossen. Dieser Unterschied ist scheinbar er beruht auf folgenden Faktoren Vor allen Dingen ist zu erwähnen, dass alle während eines Kalenderjahres gepflegten Patienten separat für dieses Jahr verzeichnet werden — ein Patient der kurz vor dem Jahreswechsel aufgenommen oder kurz danach entlassen wurde tritt also zweimal in Erscheinung wenn die Patientenzahlen verschiedener Jahre addiert werden. Es sind ferner einige unklare Fälle unbeachtet geblieben auch waren eine Reihe von Anamnesen im Archiv des Krankenhauses nicht auffindbar Schliesslich blieben einige Fälle unbeachtet, weil der betr Patient nicht in Helsinki zuhause war Die Resultate der Tabellen sind statistisch getestet nach der "chi square" Methode (x^2)

nachweisen verursacht das Einatmen von Tabakrauch bei Angina pectoris-Patienten periphere Vasokonstriktion und anginöse Beschwerden Graybiel u.a. (61) *haben gezeigt, dass* das Rauchen den Blutdruck erhöht und gleichzeitig Veränderungen der T — Welle hervorruft. Segal (157) hat darauf hingewiesen dass das Zigaretten-Rauchen die Herztätigkeit anregt und eine Abflachung der T — Welle verursacht, sowie dass der Effekt der Filterzigaretten sich nicht von dem der anderen unterscheidet U.a. hat auch Bryant (26) konstatiert, dass der Tabakgenuss kleine Veränderungen der T Welle verursacht, er ist jedoch der Ansicht dass dies nicht auf Ischämie sondern auf erhöhte Herztätigkeit zurückzuführen ist. Dieses Phänomen zeigte sich sowohl bei Gesunden wie bei Angina Pectoris-Patienten. Nach Ansicht des Autors hat der kardiovaskuläre Effekt des Tabakgenusses eine äusserst starke invidueIle Variationsbreite Wie u.a. Tannenbaum (166) zeigt kam es bei 15 % gesunder Personen unter 40 Jahren und bei 25 % bei Personen über 40 Jahren nach Tabakgenuss zu ballistokardiographischen Veränderungen. Buff (27) gibt eine etwas niedrigere Zahl an, Russek (149) eine etwas höhere. Russek (149) weist ausserdem darauf hin, dass der coronare Blutumlauf durch Tabak vermindert, durch Alkohol dagegen erhöht werde. Davis u.a (36) vergleichen in einer Arbeit die ballistokardiographischen Werte von Gesunden und Coronarpartienten. *Der Zigarettentest* war bei 7,5 % der Gesunden und bei 48,9 % der Coronarpatienten positiv

Praktizierende Ärzte können häufig beobachten, dass mässige Alkohol*mengen bei Anfällen von Angina pectoris* von direkt günstiger Wirkung sind. Dieses Faktum ist auch bei White und Sharber (177) sowie bei Falck (50) betont. Über das Risiko des Auftretens von Herzinfarkten bei Alkoholgenuss berichten Fitzhugh und Hamilton (51) und teilen 5 Infarktfälle in Zusammenhang mit Al*kohol Excess* mit. *Blumer (17)* bezweifelt dass Alkohol in mässigen Mengen genossen, ein erhöhtes Infarktrisiko mit sich bringe die gleiche Meinung äussern Master Dack und *Jaffe* (109) Glendy u.a. (54) sowie Sprague (161)

14 % der Fälle von Blumers Material (17) genossen nach eigener Angabe *regelmässig Alkohol*, während sich 52 % als Abstinenzler bezeichneten. In einem Kontrollmaterial von Gesunden kam der Autor zu etwa demselben Resultat 64 4 % der Patienten im Material von White und Sharber (177) bezeichneten sich als Abstinenzler während 1,1 % erhebliche Alkoholmengen zu sich nahmen. Im Material von Yater u.a. *(186)* ergeben sich ungefähr die gleichen Zahlen — *50 %* der erfassten Infarktpatienten genossen Akohol, aber nur 6 von 450 Patienten in erheblichem Umfang Das Material von Gertler u.a. (53) erbrachte bei den Infarktpatienten einen kleineren Alkohol geniessenden Prozentsatz als in einem Kontrollma*terial. Das Material von Räsänen* (151) ergab bei männlichen Infarkt

Tabelle 3

Nach den Jahresberichten

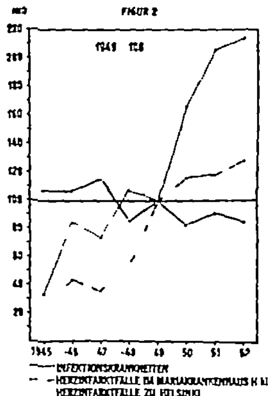
Jahr	Gesamtzahl der Pat. der Abt. f. Innere Med. (A)	Einwohnerzahl von Helsinki (B)	Infarkt fälle	% von A	% von B	Todes- fälle bei Infarkt	% A	% B	Mortalität
1945	14346	302463	58	0 40	0 019	21	0 15	0 007	38,8
1946	11804	332309	147	1,25	0,044	60	0,51	0 018	40,8
1947	12096	337526	130	1 07	0,039	42	0,35	0 012	32,3
1948	11489	340980	188	1 64	0 055	67	0,58	0 020	35 6
1949	11640	350426	176	1,51	0,050	58	0,50	0 011	32,9
1950	13624	364004	292	2 14	0 080	52	0,38	0,014	17,8
1951	12902	374019	363	2,81	0 091	92	0 71	0,025	25,3
1952	11702	383858	376	3,21	0 098	73	0 62	0 019	19,6

Übersicht über die Herzinfarktfälle di in den städt. Krankenhäusern von Helsinki behandelt wurden. Nach den Jahresberichten.

(Bettenzahl) nicht möglich war hat die ansteigende Tendenz in gewissem Umfang Einfluss auf die Zusammensetzung des Patientenmaterials ausgeübt.

Aufschlussreich dürfte ein Überblick über das Verhältnis der steigenden Herzinfarktfrequenz und die allgemeine Krankheitslage von Helsinki sein. Zum Vergleich wurden die — meldungspflichtigen — Infektionskrankheiten herangezogen.

Figur 2 zeigt die Frequenz von Infarktfällen im Maria Krankenhaus und den städt. Krankenhäusern von Helsinki und die Frequenz der Infektionskrankheiten in Helsinki in der Zeit 1945—1952. Die Kurven wurden nach einem Index mit Basis 100 für das Jahr 1949 ausgearbeitet. Die absoluten Werte und die Indexzahlen gehen aus Tab 4 hervor Die Kurve für alle städt. Krankenhäuser von Helsinki zeigt einen steileren Anstieg als die des Maria Krankenhauses



Die Frequenz der Inf ktionskrankheiten und der Herzinfarktfälle in Helsinki sowie der Herzinfarktpatienten im Maria Krankenhaus zu Helsinki für den Zeitraum 1945—1952.

lationsuntersuchung dass das Risiko für Coronarerkrankungen bei Personen mit Hypercholesterolämie grösser ist als normal. Nikkilä (1?7) hat im Blut von Herzinfarktpatienten einen bedeutend höheren Cholesterolspiegel nachgewiesen als bei den Personen eines Kontrollmaterials Karvonen (84) teilt mit dass Finnen eine Ten denz zu hohen Cholesterolwerten haben und dass die Mortalität bei Blut kreislaufleiden in Finnland hoch ist

Es dürften in diesem Zusammen hang ein paar Worte zum Zusammen hang von Coronarsklerose und Herz infarkt angebracht sein. Verschiedene Forscher sind der Ansicht, dass die Coronarsklerose der gewöhnlich ste Grund für das Auftreten von Herzinfarkten ist. Appelbaum und Nicolson (5) konstatierten dass 90 % der an Herzinfarkt verstorbenen Pa tienten eine Coronarsklerose gehabt hatten. Unter 300 Fällen von Coronarinfarkt fand Bean (7) bei 96 % generalisierte Arteriosklerose und bei 98,2 % der Fälle Coronarsklerose. v Bonsdorff (20) hat davor gewarnt, ohne hinreichenden Grund Atherosklerose zu diagnostizieren. Bei 450 Herzinfarktfällen konstatierten Yater u.a. (186) in 100 % der Fälle mikroskopische Arteriosklerose der Kranz arterien. Thompson (169) hat darauf hingewiesen, dass Coronarthrombose im allgemeinen auf Atherosklerose zurückgeht und dass die schliessliche Thrombosierung mehrere Tage dauern kann, weshalb er eine präventive Behandlung mit Antikoagulantien warm anempfiehlt. Enos u.a. (49) konstatierten bei der Obduktion junger Gefallener des Koreakrieges zahlreiche Fälle von Coronarsklerose Duguid und Robertson (43) waren der Ansicht dass Atherosklerose nicht zu einer Verschlechterung des Coronar blutkreislaufes zu führen braucht. Nach Page u.a. (132) zeigten Obduktionen, dass die Zunahme der Coronarskleroseflälle nicht so gross war wie die der Coronarinfarktfälle.

Eine Reihe von Forschern hat die Frequenz der Blutkreislauferkrankungen bestimmter Bevölkerungsgruppen bei verschiedenartiger Lebensmittelversorgung beobachtet. In mehreren Arbeiten der Jahre 1934—193? haben Master u.a. (105 106 107 108) darauf hingewiesen, dass eine Diät mit niedrigem Kaloriengehalt bei Coronarsklerosepatienten einen günstigen Effekt hat. Biörck und Blomquist (12) zeigten einen markanten Rückgang der Mortalität kardiovaskulärer Erkrankungen in Schweden während der kriegsbedingten schlech ten Versorgungslage. Malmros (102) hat hervorgehoben, dass fettreiche Kost die Cholesterolresorption des Darms fördert, und dass während der Kriegsjahre der Fett und Eierkon sum in Schweden und Norwegen, nicht aber in Dänemark zurückgegangen sei. Für dieselbe Zeit verzeichnet er einen Rückgang der Herzinfarkt fälle in Schweden und Norwegen nicht aber in Dänemark. Wie Hen schen (71) mitteilt, zeigte die Mortalität bei den Diagnosen Arteriosklerose und Myokarditis chron., unter welche auch der Coronarinfarkt fällt, wäh rend der Jahre 1928—1941 in Stock holm ein stetes Ansteigen. Der für

und die Therapie wird besser. Es erscheint deshalb angezeigt, die Mortalität im Material des Maria Krankenhauses etwas genauer zu beleuchten. Um für die statistische Bearbeitung etwas grössere Einheiten zu erhalten, habe ich das Material in 2 Gruppen gegliedert, u.zw. in die Patienten der Jahre 1945—1948 und die der Jahre 1949—1952. Jede Gruppe umfasst also vier Jahre. Dass die Grenze zwischen 1948 und 1949 gezogen wurde ist darauf zurückzuführen, dass — wie die Betrachtung der Frequenzzunahme zeigt — gerade während dieser Jahre eine beträchtliche Zunahme erfolgte. Tabelle 5 verzeichnet die Mortalität in unserem Material während der beiden Perioden, und die statistische Untersuchung zeigte deutlich, dass die Mortalität während der ersten Periode bedeutend grösser war als während der zweiten.

Tabelle 5

	1945-1948		1949-1952		Insgesamt	
Überlebende	71	54%	325	74%	396	70%
Tote	60	46%	113	26%	173	30%
Summe	131	100%	438	100%	569	100%

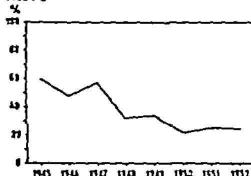
Die Mortalität während der Jahre 1945—1948 und 1949—1952

Nachdem während der zweiten Beobachtungsperiode ein deutlicher Rückgang der Mortalität festgestellt werden konnte, erscheint es aufschlussreich, die Entwicklung der Mortalität von Jahr zu Jahr zu verfolgen. Tabelle 6 gibt den Anteil der Verstorbenen im gesamten Patientenmaterial während der Jahre 1945—1952 mit dem Index des Mortalitätsprozentsatzes.

Tabelle 6

	Patienten insgesamt		davon Verstorben		Mortalität %		Mortalitätsindex 1949=100
1945	15		9		60		176
1946	42		20		48		141
1947	30		17		57		168
1948	44	131	14	60	32	46	94
1949	87		30		34		100
1950	110		23		21		62
1951	108		27		25		74
1952	135	438	33	113	24	26	71
		569		173		30	

Die Entwicklung der Mortalität während der Jahre 1945—1952



Die Entwicklung der Infarktmortalität im Zeitraum 1945—1952 (auf prozentualer Basis)

Aus der Tabelle und den Kurven ergibt sich, dass die Mortalität recht starke jährliche Schwankungen auf

führte zu einem direkt entgegengesetzten Resultat. Auch die Nahrung der Eskimos ist überaus reich an Protein, Fett und Cholesterin, aber Gefäss-Sklerose war dort seltener als z.B. in Finnland. Zu beachten bleibt dass das Fett, das die Eskimos verzehren grösstenteils von Seetieren stammt. Ehrström war der Ansicht, dass wahrscheinlich spezifische Faktorenkonstellationen erforderlich sind bevor eine protein-, fett- und cholesterinreiche Nahrung sklerosefördernd werden kann. Dieselbe Ansicht vertritt Schmidt (154), der darauf hinwies, dass sowohl Lappen wie Eskimos im Winter ausschliesslich von Fett leben. Er zeigte ferner, dass während der deutschen Besetzung von Norwegen die Gefässkrankheiten zurückgingen, und dass gleichzeitig die totale Kalorienmenge der Nahrung (also nicht nur der Fettkonsum) kleiner wurde sowie, dass man vom Weizenbrot zum Vollkornbrot überging. Bekanntlich enthält unvermahlenes Korn E-Vitamin, das jedoch im Weissbrot nicht enthalten ist. Die Bantus verzehren Maisbrot, welches E-Vitamnin enthält. Beim Vergleich von Kuczynskis, Schmidts und Ehrströms Publikationen (90, 154, 45) ergibt sich, dass ersterer von fetten Individuen spricht, während wenigstens die Lappen ein magerer Volksstamm sind, letzteres dürfte auch auf die Eskimos zutreffen. Nach Duguid u.a. (42, 43) sollte der Kost keine zu grosse Aufmerksamkeit geschenkt werden, da auch andere Faktoren einwirken. Zu diesem Resultat sind auch Doyle u.a. (41) gekommen. Keys (88) hebt den hohen Fettkonsum der Finnen hervor: die Infarktsterblichkeit ist in Finnland ebenso hoch wie in den USA, obwohl die Finnen ein sportliches Volk sind und sich im allgemeinen genügend bewegen. Yudkin (187) äussert die Ansicht, dass sichere Beweise für den Anteil des Fetts an den Ursachen des Herzinfarkts nicht beizubringen sind, es sei jedoch erwiesen, dass physische Bewegung gegen Infarkte schützen könne.

Verschiedene geographische Gebiete haben deutliche Unterschiede im Auftreten von Coronarerkrankungen gezeigt, und es ist die Ansicht geäussert worden, dass dies auf den verschiedenen Verhältnissen in der Ernährung beruhe. So etwa haben Sjövall und Wihman (159) konstatiert, dass bei Frauen in Lund Sklerosen häufiger waren als bei Frauen in Stockholm; die Autoren weisen gleichzeitig darauf hin, dass es in Lund mehr korpulente Frauen gibt als in Stockholm. Nach Lundquist und Bjornwall (98) trat in Südschweden häufiger Arteriosklerose auf als in Nordschweden. Wie Steiner (162) angibt, ist Coronarsklerose auf Okinawa äusserst selten. Die Ernährung besteht auf Okinawa hauptsächlich aus Kohlehydraten. Yater u.a. (186) konnten keine Ernährungsunterschiede zwischen einem Infarktmaterial und einer Kontrollgruppe feststellen und hielten Korpulenz nicht für einen wichtigen ätiologischen Faktor. Malmros (103) hat darauf hingewiesen, dass der Fettverbrauch in Italien geringer ist als in Schweden und dass

Tabelle 8

Alter	Männer				Frauen			
	Patienten		Gesamt	Index	Patienten		Gesamt	Index
	Anzahl	%	bevölk. %		Anzahl	%	bevölk. %	
35—39	10	2.8	20.3	13	2	1 0	17 1	6
40—44	20	5.5	20 9	26	7	3 4	18 0	19
45—49	40	11 0	17 6	63	17	8.2	15.2	54
50—54	61	16.9	13.3	127	18	8 7	13.2	66
55—59	77	21.3	10.5	203	17	8.2	11.1	74
60—64	72	19.9	7 6	262	46	22.2	9.3	239
65—69	45	12.4	4 8	258	37	17.9	6.9	259
70—74	19	5.2	2.9	179	34	16 4	4.7	349
75—79	13	3 6	1 4	257	21	10 1	2.8	361
80 u. mehr	5	1 4	0 7	200	8	3.9	1 7	229
Total	362	100 0	100 0	100	207	100 0	100 0	100

Gliederung des Materal nach Alter und Geschlecht im Vergleich mit der Gesamt bevölkerung von Helsinki (für das Jahr 1950)

Aus Tabelle 8 ergeben sich die Werte nach denen Figur 4 ausgearbeitet wurde

Wie diese Figur zeigt, ist der Anteil der älteren Jahrgänge im Material bedeutend grösser als der Anteil der entspr Gruppen an der Bevölkerung in Helsinki die Erkrankung ist somit bei älteren häufiger als bei jüngeren Personen. Es ergibt sich ferner dass Infarkte bei jüngeren Personen mehr Männer bei älteren mehr Frauen befallen.

Da während der in vorliegendem Material erfassten 8 Jahre eine spürbare Frequenzzunahme aufgetreten ist dürfte es aufschlussreich sein zu untersuchen inwieweit innerhalb dieses Zeitraums eine allgemeine Verschiebung der Altersgruppen auf getreten ist. Denkbar wäre ja dass sich als eine der Ursachen dieser Frequenzzunahme der Umstand erweist dass jüngere — somit grössere — Jahrgänge während des späteren Teils der Beobachtungsperiode in grösserem Umfang befallen worden sein könnten.

Um klarzustellen, ob in Bezug auf die Altersklassen Verschiebungen im Material vorkommen, wurde Tabelle 9 errechnet. Die Patienten wurden in die Altersgruppen *unter 50 J., 50—59 J 60—69 J* sowie *70 J und mehr* gegliedert. In Klammern werden ausserdem Patienten unter 40 J aufgeführt. Da jedoch für Periode I (1945—1948) hier nur ein Fall auftrat, wurde dieser mit der folgenden Gruppe — unter 50 J — zusammengelegt

äussert schlecht war seltener auftrat. Lups und Francke (89) konstatierten während der Kriegs- und Hungerjahre bei 520 Personen eine fallende Tendenz des Blutdrucks. Dieselbe Feststellung machte Tarejew (167) während des Krieges bei der Leningrader Bevölkerung.

Zusammenfassend können wir feststellen, dass sowohl das Auftreten von Sklerose — und damit Coronarsklerose — wie von Herzinfarkt bei Volksgruppen mit schlechter Versorgungslage deutlich absinkt. Ferner konnte gezeigt werden, dass Herzinfarkte bei solchen Völkern seltener sind, die in ärmlichen Verhältnissen leben. Im Zusammenhang mit der Erhöhung des sozialen Standards pflegt der Anteil des Fettes und des Cholesterols an der Nahrung zu steigen.

Infektionskrankheiten — siehe Figur 2 — während des Beobachtungszeit raums zurückgegangen ist und vor allem, nachdem sich die Behandlung dieser Krankheiten durch Einführung der Antibiotika völlig verändert hat, ging der Bedarf an Pflegeplätzen für solche Krankheiten entsprechend zurück, wodurch sich die Möglichkeiten zur Aufnahme anderer innermedizi nische Fälle verbesserten. Es ist nicht ausgeschlossen, dass die aus Tab. 10 ersichtliche Altersverschiebung z.T hierauf beruht da jedoch während des gesamten Zeitraumes ein Herzinfarkt absolute Aufnahmeindikation war lässt sich Tab 9 kaum mit Tab 10 vergleichen.

Tabelle 11

Jahr	Alter unter 50	51—69	70 u. mehr	Summe
1945	79,6	17,3	3 1	100 %
1946	79 4	17,5	3,1	100 %
1947	79,0	17 7	3,3	100 %
1948	78 4	18,2	3 4	100 %
1949	77,9	18 6	3,5	100 %
1950	77,5	18,9	3 6	100 %
1951	77,2	19 1	3 7	100 %
1952	77 0	19,2	3,8	100 %

Die Altersgruppierung der Bevölkerung von Helsinki während der Jahre 1945—1952.

Es ist in diesem Zusammenhang aufschlussreich noch zu erfahren in wieweit auch bei der Bevölkerung in Helsinki während dieser Periode eine Zunahme der über 70-jährigen Personen stattgefunden hat, wodurch die Zuwachsrate alter Personen des Materials eine natürliche Erklärung fände

Aus diesem Grunde wurde Tabelle 11 zusammengestellt aus welcher sich sodann ergibt, dass die Bevölkerung in Helsinki keine dement sprechende Zunahme der Personen über 70 J aufweist.

Eine weitere interessante Frage ist es inwieweit sich das prozentuale Verhältnis der Geschlechter während der Beobachtungszeit innerhalb des Materials verändert hat. Tabelle 12 gibt die Zusammensetzung nach Geschlechtern während der beiden Beobachtungsperioden an.

Tabelle 12

	1945—1948	%	1949—1952	%	Summe	%
Männer	79	60	283	65	362	64
Frauen	52	40	155	35	207	36
	131	100	438	100	569	100

Die prozentuale Verteilung der Geschlechter während der Perioden 1945—1948 und 1949—1952.

Bei einem statistischen Test konnte die leichte Zunahme der Männer um 5 % bei Periode II nicht für signifikant gehalten werden. Zieht man hierneben in Betracht, dass der weibliche Bevölkerungsteil von Helsinki während dieser Jahre ein geringes Absinken zeigt, so darf man der An sicht sein, dass die prozentuale Ver teilung der Geschlechter während der beiden Beobachtungsperioden im grossen ganzen unverändert war

Nicht unwesentlich dürfte es sein, klarzustellen, wie sich die Mortalität auf Geschlechter und Altersgruppen verteilt. Hierzu dient Tabelle 13

relation zwischen dem Ansteigen der Herzinfarktfrequenz einerseits und Bevölkerungsbewegung Alter und Geschlecht der Patienten Entwick lung der Mortalität der Infarktpatien ten während der Beobachtungszeit, Zeitpunkt der Erkrankung Sozial gruppen, Familienstand Auftreten früherer stenokardischer Beschwer den, Rückfall, hoher Blutdruck sowie Alkohol und Tabakkonsum der Infarktpatienten anderseits

Auf die Cholesterolfrage wollte ich — und konnte ich — nicht eingehen, weil diese Arbeit auf Krankenhaus-journalen fusst die im allgemeinen keine Angaben über den Cholesterol spiegel enthalten Da sich allerdings die Versorgungslage während des B›obachtungszeitraums grundlegend wandelte — s.o. — lag mir daran, wenigstens das Verhältnis des An stiegs der *Herzinfarktfrequenz* zu dem gestiegenen Butter Zucker und Fleischverbrauch zu untersuchen.

Im Zusammenhang mit dieser Un tersuchung wollte ich ferner soweit möglich, die ätiologische Bedeutung verschiedener sozialer und medi zinischer Faktoren für den Herzin farkt erforschen.

Zeitpunkt der Erkrankung

Wie der Überblick über das Schrifttum zeigte waren die verschiedenen Forscher über das Verhältnis der Jahreszeiten zu der Infarktfrequenz verschiedener Meinung Das Material ist in Tabelle 15 je nach dem Erkrankungszeitpunkt monatsweise zusammengestellt. In zehn Fällen konnte das Erkrankungsdatum nicht mit Sicherheit eruiert werden da die vom Infarkt hervorgerufenen Beschwerden nicht so schwerwiegend waren, dass der betr Patient sich sofort in Pflege begab

Tabelle 15

	Männer	%	Frauen	%	Summe	%
Januar	29	8	18	9	47	8
Februar	21	6	12	6	33	6
März	28	8	12	6	40	7
April	27	8	10	5	37	7
Mai	41	11	17	8	58	11
Juni	19	5	17	8	36	6
Juli	28	8	6	3	34	6
August	31	9	8	4	39	7
September	23	6	24	12	47	8
Oktober	34	10	27	13	61	11
November	37	10	22	11	59	11
Dezember	39	11	29	15	68	12
	357	100	202	100	559	100
unbekannt	5		5		10	
	362		207		569	

Das Material nach dem Erkrankungsmonat.

Um den Überblick über die Frequenz während der einzelnen Monate anschaulicher zu machen wurde Figur 5 ausgearbeitet. Hierbei wurde für die Monatsfrequenz ein Index berechnet, als dessen Basis der theoretische Monatswert d.h. 1/12 aller Fälle, herangezogen wurde. Wie die Figur zeigt, liegt die Frequenz der Periode Februar—August klar unter dem Mittelwert. Eine Ausnahme bildet lediglich der Mai, dessen Index ungefähr dieselben Werte erreicht wie die Herbstmonate. Trotz des hohen Maiwertes verbleibt die Quartalsfrequenz für April—Juni geringer als es der theoretische Wert (1/4 aller Fälle) erwarten liesse Dasselbe gilt für die anderen Quartale ausser für Oktober—Dezember mit einem den theoretischen kräftig übersteigenden Wert. Dass als Wintermonate Januar—März gewählt wurden erklärt sich daraus dass Helsinki eine Küstenstadt ist, und dass die eigentliche Kälteperiode hier im allgemeinen erst mit dem Monatswechsel Dezember—Januar einsetzt. Figur 5 enthält ausserdem zwei weitere Kurven durch die die monatliche Frequenz während jeder der beiden Beobachtungsperioden angegeben sind. Diese Kurven zeigen ungefähr denselben Verlauf, so dass auf eine Verschiebung der monatlichen Frequenzen während des Beobachtungszeitraumes kaum geschlossen werden kann. Dies ergibt sich auch aus Tabelle 16 die nach der prozentualen Verteilung des Materials während der einzelnen Monate ausgearbeitet wurde

V EIGENE UNTERSUCHUNGEN

Zum Frequenzanstieg des Herzinfarkts im Zuständigkeitsgebiet des Maria Krankenhauses

Im Verlauf der Jahre 1945—1952 ist die Anzahl der wegen Herzinfarkt aufgenommenen Fälle im Maria Krankenhaus um das Neunfache gestiegen. Gegenüber 15 Patienten 1945 wurden 1952 135 Pat. gepflegt. Tabelle 2 gibt einen Überblick über die Zahlenverhältnisse während der einzelnen Jahre und verzeichnet gleichzeitig die Totalanzahl der Patienten auf den innermedizinischen Abteilungen des Krankenhauses

Tabelle 2

Jah	Totalanzahl der Patienten	Herzinfarktfäll Anzahl	%
1945	2138	15	0 70
1946	2092	42	2,00
1947	2262	30	1,32
1948	2259	44	1,94
1949	2242	87	3,88
1950	2216	110	4,96
1951	2137	106	4,96
1952	2151	135	6,27

Anzahl der Herzinfarktpatienten im Maria Krankenhaus 1945—1952 und deren prozentualer Anteil am Gesamtpatientenbestand.

Wie die Tabelle (2) zeigt, trat während des Beobachtungszeitraums eine erhebliche Zunahme der Herzinfarktpatienten auf. Nur das Jahr 1947 bildete eine Ausnahme Die Zunahme von 0 7 % auf 6,27 % ist so gross dass sie in gewissem Umfang auf die Struktur des Patientenbestandes der innermediz. Abteilungen überhaupt eingewirkt hat. Auf Grund der Zunahme der Infarktpatienten im Maria Krankenhaus dürfte ein Vergleich mit einem grösseren Material aufschlussreich sein. Tabelle 3 bringt deshalb eine Zusammenstellung von Angaben aus den Jahresberichten der städt. Krankenhäuser von ganz Helsinki, usw betreffen diese Angaben von 1945 an ausser dem Maria Krankenhaus auch das Aurora und das Krankenhaus Kivelä (Stengård) von 1946 an trat mit der Eingemeindung der Gemeinde Malm auch noch das dortige Krankenhaus hinzu.

Aus der Tabelle ergibt sich dass die Bevölkerung von Helsinki während des erfassten Zeitraums um 27 0 % gestiegen ist. Die Anzahl der in Krankenhauspflege befindlichen Herzinfarktfälle ist gleichzeitig um 548 % gestiegen. Nachdem eine Erhöhung der Pflegeplätze

Tabelle 17

Tageszeit	Uhrzeit	Stundenzahl	Anzahl der Pat.	Theoretischer Wert	Abweichung
Morgen	6—9	3	58	35	23
Vormittag	9—12	3	31	35	—4
Nachmittag	12—16	4	63	47	16
Abend	16—22	6	67	71	—4
Nacht	22—6	8	64	95	—31
		24	283	283	0
		unbekannt	286		
			569		

Aufgliederung des Material nach der Tageszeit der Erkrankung

Die Tabelle zeigt dass während der Morgenstunden zwischen 6—9 Uhr bedeutend mehr Erkrankungen auftraten als sich nach den theoretischen Werten erwarten liesse. Eine ähnliche allerdings weniger starke Zunahme liegt in der Zeit zwischen 12—16 Uhr Die Nachtfrequenz hingegen bleibt merkbar unter dem Mittelwert. Beim statistischem Test erwies sich dieses Resultat als signifikant.

Nachdem sich für Morgen und Nachmittag eine klare Frequenzzunahme ergibt, dürfte es aufschlussreich sein zu überprüfen ob die Mortalität dieser Patienten mit derjenigen der zu anderen Tageszeiten erkrankten übereinstimmt. Es wurde hierfür Tabelle 18 ausgearbeitet die zu verschiedenen Tageszeiten erkrankten Patienten sind hier als Überlebende und Verstorbene angegeben. Die Tabelle zeigt, dass die Mortalität der morgens und nachmittags erkrankten Patienten geringer ist als die der zu anderen Tageszeiten erkrankten. Leider muss das Material aber als zu klein angesehen werden, um als statistisch signifikant gelten zu können.

Tabelle 18

	Morgen %	Vormittag %	Nachmittag %	Abend %	Nacht %
Verstorbene	16	29	19	27	28
Überlebende	84	71	81	73	72
	100	100	100	100	100

Zusammenfassend kann man hinsichtlich der Monate der Erkrankung sagen, dass die Monate Mai Oktober November und Dezember im vorliegenden Material eine klar überdurchschnittliche Frequenz aufweisen. Die

Tabelle 4

Jahr	Infarktpat. im Maria Krankenhaus Innen mediz. Abt. (nach der amtl. Statistik)		Infarktpat. der städt. Krankenhäuser Helsinki		Infektionskrankheiten Helsinki (meldepflichtig)	
	Anzahl	Index	Anzahl	Index	Anzahl	Index
1945	22	21	58	33	39550	107
1946	46	43	147	84	39555	107
1947	38	36	130	74	42392	115
1948	58	54	188	107	31862	86
1949	106	100	176	100	36880	100
1950	123	116	292	166	30587	83
1951	125	118	363	206	33401	91
1952	136	128	376	214	31398	85

Anzahl der Infarktpatienten im M ria-Krankenhaus, in den städt. Krankenhäusern von Helsinki und Infektions-Krankheiten im Gebiet on Helsinki während d J 1945—1952

was z.T. darauf zurückzuführen ist, dass Aurora und Malm mehr Patienten als früher aufnehmen konnten.

Wie die Figur zeigt, nimmt die Kurve für Infektionsfälle einen etwas ungleichmässigen Verlauf. Es ergibt sich indessen, wenn man die für diese Zeit aufgetretene Bevölkerungszunahme in Betracht zieht, eine fallende Tendenz. Die beiden Infarktkurven ergeben ein ganz anderes Bild — hier ist ein deutlicher Anstieg unverkennbar und dieser ist offenbar nicht auf die Bevölkerungszunahme zurückzuführen. Im Vergleich mit der Tendenz der Infektionsfälle muss diese Zunahme überraschend wirken.

Zusammenfassend ist festzustellen, dass die Zahl der Herzinfarktpatienten im Maria-Krankenhaus während der Jahre 1945—1952 gestiegen ist. Eine klare Zunahme lässt sich auch für die städt. Krankenhäuser von Helsinki insgesamt feststellen. Dieser Anstieg steht nicht in Proportion zur Bevölkerungszunahme von Helsinki. Die Frequenz der Infektionskrankheiten hatte zu gleicher Zeit fallende Tendenz.

Mortalität

Eine nähere Betrachtung von Tabelle 3 lässt erkennen, dass sich die Zahl der in den städt. Krankenhäusern von Helsinki während der Jahre 1945—1952 gepflegten Herzinfarktfälle im Verlauf dieser Zeit um 548 % erhöht hat. Werden nur die Todesfälle durch Herzinfarkt in Betracht gezogen, so ergibt sich eine Frequenzerhöhung um 248 %. Ein Rückgang der Mortalität geht nach allgemeiner Meinung auf zwei Ursachen zurück: Die zur Pflege gelangenden Fälle sind weniger schwer

wäre Dieses Übergewicht der Gruppe I erwies sich als signifikant auch bei statistischem Test Es ist allerdings hierzu leider eine Bemerkung erforderlich in der Statistik über die Bevölkerung von Helsinki ist die Gruppe "berufslose Gattin" ganz weggelassen während die im Material des Maria Krankenhauses auftreten den Ehefrauen der Sozialgruppe ihres Mannes zugerechnet sind. Wird nun allerdings der männliche Teil der Patienten von Sozialgruppe I des Maria Krankenhauses mit den Zahlen für die Bevölkerung in Helsinki verglichen, so ergibt sich dasselbe Bild, so dass obige Bemerkung sachlich bedeutungslos sein mag Hinsichtlich der Sozialgruppe IV wiederum ergibt sich im Vergleich mit der Bevölkerungsstatistik ein Fehlbetrag von Infarktfällen. Auch dieser Umstand hat sich bei statistischem Test als signifikant erwiesen. Das Material des Maria Krankenhauses stützt demnach die Theorie einer Krankheit der "Wohlhabenden Eine weitere Angabe von Tabelle 19 dürfte interessant sein nämlich die Anzahl der Frauen in Sozialgruppe IV Bei den Männern ergibt sich in dieser Gruppe ein Wert von nur 18 % bei den Frauen demgegenüber von 27 % Um klarzustellen inwieweit Gruppe IV mehr weibliche Patienten aufweist als die anderen Gruppen, wurde Tabelle 20 ausgearbeitet.

Tabelle 20

	I	II	III	IV	Alle
Männer %	68	72	66	52	65
Frauen %	32	28	34	48	35
	100	100	100	100	100

Verhältnis der Geschlechter in den Sozialgruppen.

Die Tabelle zeigt, dass im Material unter Sozialgruppe IV verhältnismässig mehr Frauen auftreten als im ganzen Material und auch als in den anderen Gruppen. Der statistische Test war in dieser Hinsicht signifikant. Leider stehen statistische Angaben darüber welches prozentuale Verhältnis zwischen Männern und Frauen im Hinblick auf die Sozialgruppen in der Stadt Helsinki besteht, nicht zur Verfügung sodass nicht untersucht werden konnte ob Frauen dieser Sozialgruppe (IV) häufiger an Infarkt erkrankten als die Frauen anderer Gruppen.

Konstatieren konnte man lediglich, dass im vorliegenden Material in Sozialgruppe IV verhältnismässig mehr Frauen auftreten als in den anderen Sozialgruppen.

Da bei den Untersuchungen zur Tageszeit in der die Infarktfälle auftraten, eine Frequenzzunahme für die Morgenstunden (6—9 Uhr) und die Nachmittagsstunden (12—16 Uhr) beobachtet wurde, erschien es aufschlussreich, festzustellen, inwieweit sich die Erkrankungszeiten bei den Sozialgruppen bemerkbar machen. Zu diesem Zweck wurde Tabelle 21 angelegt, in der die Sozialgruppen I und II sowie III und IV als je eine Gruppe auftreten. Das Material wurde wieder nach den betr Tageszeiten gegliedert, wodurch sich die nachstehende prozentuale Verteilung ergab

weist doch ist die allgemeine Entwicklung eindeutig fallend. So ist der Mortalitätsindex nach 1948 in keinem Jahr mehr über 100 gestiegen, obwohl er vorher einen Mindeststand von 141 zeigte Auch statistisch hat sich der Mortalitätsrückgang als markant erwiesen.

dies unter Umständen auf der bevölkerungsmässigen Verteilung — mehr Frauen als Männer dieser Altersklassen — beruhen könnte musste ein Vergleich mit der entspr Altersklasse der Bevölkerung in Helsinki angesetzt werden.

Zu diesem Zweck wurde Figur 4

Tabelle 7

	Unter 50 J	%	50—60	%	60—70	%	70 J und mehr	%	Total	%
Männer	70	73	138	80	117	58	37	37	362	64
Frauen	26	27	35	20	83	42	63	63	207	36

Das Material nach Alter und Geschlecht

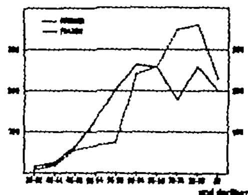
Alter und Geschlecht

Nach dem Schrifttum sind vor allem die mehr als 50-jährigen Herzinfarkten ausgesetzt, auch ist maskuline Dominanz deutlich. Tabelle 7 bringt eine Gliederung des Materials nach Alter und Geschlecht.

Nach Tabelle 7 enthält das Material 362 Männer und 207 Frauen, d.h. 64 % bzw 36 % und somit eine klare Dominanz der Männer Was das Alter betrifft, so waren nur 96 Patienten unter 50 Jahre alt (16,9 %) während 473 50 Jahre alt und älter waren (83,1 %) Die stärkste Altersgruppe der Männer waren die 50—60-jährigen, bei den Frauen die 60—70-jährigen. Die Dominanz der Geschlechter wechselt stark zwischen den einzelnen Altersgruppen. Trotz der aufs Ganze gesehen männlichen Dominanz herrscht bei den Patienten über 70 J weibliche Dominanz. Da

ausgearbeitet. Der prozentuale Anteil der jeweiligen Altersgruppen an der Bevölkerung von Helsinki ist mit 1 bezeichnet worden die Kurven geben an, inwieweit der Anteil der Altersgruppe im vorliegenden Material unter bzw über den Bevölkerungsziffern liegt.

FIGUR 4



Verhältnis der Bevölkerung von Helsinki im Jahre 1950 (= 1,0) und der Patienten im vorliegenden Material Gliederung nach Altersgruppen.

Familienstand

Zweifellos übt die Ehe auf die Lebensgewohnheiten einen beträchtlichen Einfluss aus. Aus diesem Grunde wurde der Familienstand der Patienten in vorliegender Untersuchung einer genaueren Prüfung unterzogen. Tabelle 22 bringt einen Vergleich zwischen den weiblichen Patienten des Materials und dem Anteil der Frauen an der Bevölkerung von Helsinki, wobei das Material in drei Gruppen eingeteilt wurde — in Unverheiratete Verheiratete und in Verwitwete bzw Geschiedene.

Tabelle 22

	40—49		50—59		60—69		70—	
	Material %	Helsinki %	Material %	Helsinki %	Material %	Helsinki %	Material %	Helsinki %
ledig	8	25	11	28	16	27	24	25
verh.	70	59	74	45	43	28	15	13
übrige	22	16	15	27	41	45	61	62
	100	100	100	100	100	100	100	100

Die Frauen des Materials nach Familienstand und Alter verglichen mit der weibl Gesamtbevölkerung von Helsinki (1950)

Figur 8 bringt den Anteil der unverheirateten Frauen in anschaulicherer Form.



Der prozentuale Anteil der unverheirateten Frauen am Untersuchungs Material und an der Stadtbevölkerung von Helsinki i.J. 1950, nach Altersgruppen dargestellt.

Sowohl die Tabelle wie die Figur zeigt dass bei den Frauen des vorliegenden Materials der Anteil der unverheirateten Frauen bedeutend kleiner der der verheirateten wiederum bedeutend grösser als der entspr Anteil an der weibl. Gesamtbevölkerung von Helsinki war und zwar gilt dies für die jüngeren Jahrgänge. Bei den über 70-jährigen war ein Unterschied kaum festzustellen. Diese Resultate erwiesen sich bei statistischem Test als signifikant.

Der obengeschilderte Vergleich wurde auch bezüglich der Männer des Materials durchgeführt. Es ergab sich Tabelle 23

Tabelle 9

Alter	Periode 1945—1948 Patient.	%	Periode 1949—195. Patient	%	Differenz %
(unter 40)	(1)	(0 76)	(11)	(3)	
unter 50	17	13	79	18	5
50—59	41	31	132	30	—1
60—69	61	47	139	32	—15
70 und mehr	12	9	88	20	11

Das Material während der Perioden 1945—1948 u. 1949—1952 nach Alter gegliedert.

Nach Tabelle 9 scheinen während Periode II (1949—1957) die beiden Eckgruppen — unter 50 *J* und über 70 *J* — zugenommen zu haben. Der statistische Test ergibt dass die Zahlen eine leichte statistisch nicht signifikante Tendenz in eine andere Richtung zeigen, nämlich dass der Anteil der Patienten unter 50 *J* während Periode II im Material zugenommen hat. Die Zunahme für die Gruppe über 70 *J* ist dagegen für Periode II klar und auch statistisch signifikant.

Es ist in diesem Zusammenhang nicht uninteressant festzustellen, wie die altersmässige Zusammensetzung aller Patienten der innermedizinischen Abteilungen im Maria Krankenhaus während der Beobachtungszeit war und ob evtl. auch hier Verschiebungen aufgetreten sind. Zu diesem Zweck wurde unter Verwendung der Jahresberichte dieses Krankenhauses Tabelle 10 ausgearbeitet.

Tabelle 10

Alter	Periode 1945—48 Anzahl	Prozent	Periode 1949—52 Anzahl	Prozent	Veränderung Prozent
unter 50	4,636	54	3,194	36	—18
50—59	1 782	20	1,969	22	2
60—69	1 421	16	2,177	24	8
70 u. mehr	912	10	1,586	18	8
total	8 751	100	8,926	100	—

Altersklassenverteilung sämtlicher Patienten des Maria Krankenhauses auf den innermedizinischen Abteilungen während der Perioden 1945—1948 und 1949—1952

Die Tabelle zeigt beim Patientenbestand der innermedizinischen Abteilungen des Maria Krankenhauses während des Beobachtungszeitraumes eine allgemeine Zunahme der älteren Jahrgänge.

Ein Vergleich von Tab. 9 und Tab. 10 zeigt, dass in beiden Fällen eine Zunahme der älteren Jahrgänge stattgefunden hat, wobei allerdings nicht dieselben Gründe vorzuliegen brauchen. Denn beim Herzinfarktpatienten ist die Diagnose als solche schon eine absolute Aufnahme-Indikation, während sonst die Aufnahme von Patienten in die Innere Abtlg im allgemeinen vom Ermessen des Arztes abhängt. Nachdem die Frequenz der

Infarkt bei Männern nicht beobachtet werden konnte. Der Anteil der unverheirateten Frauen des Materials zeigt in Beobachtungsperiode II eine Zunahme, die jedoch statistisch nicht als signifikant erkannt werden konnte.

Heredität

Der Heredität ist, wie die zitierten Belege des Schrifttums zeigten, von verschiedenen Forschern eine gewisse Bedeutung für das Auftreten von Herzinfarkten beigemessen worden.

Bei 122 Fällen des vorliegenden Materials konnten in der Familie u.zw. bei den Eltern oder bei den Geschwistern, Coronarerkrankungen nachgewiesen werden. Dagegen konnte in 325 der Fälle in der engeren Verwandtschaft keine Coronarerkrankung nachgewiesen werden, und in 122 der Fälle waren keine sicheren Angaben über diesen Gegenstand erhältlich. Um eine Vorstellung darüber zu erhalten, ob die Heredität des Materials als markant zu betrachten ist, wurde ein Vergleichsmaterial zusammengestellt. Dieses Material besteht aus 263 willkürlich gewählten Patienten der innermedizinischen Abteilungen des Maria Krankenhauses während der Jahre 1945—1952. Aufgezeichnet wurden Infarktfälle der Eltern und der Geschwister. Ein Vergleich der beiden Gruppen erfolgt in Tabelle 25.

Tabelle 25

	Total	Coronarinfarkte in der Familie	%
Infarktmaterial	447	122	25
Kontrollmaterial	263	33	12,5

Das Auftreten von Herzinfarkten bei den Eltern und Geschwistern der Patienten des vorliegenden Material im Vergleich mit einem Kontrollmaterial von Nichtinfarktpatienten.

Herzinfarkte waren, wie die Tabelle zeigt, bei den Familienangehörigen der Infarktpatienten des vorliegenden Materials doppelt so oft wie bei den Patienten des Kontrollmaterials aufgetreten.

Beobachtet wurde auch das Verhältnis von Heredität und Sozialgruppe. Zu diesem Zweck wurden die Sozialgruppen I u. II sowie die Sozialgruppen III u. IV des Materials zusammengelegt, um grössere und damit zuverlässige Zahlen zu erhalten.

Tabelle 26

MÄNNER Sozialgruppe	Heredität + Anzahl	%	Heredität — Anzahl	%	Gesamt Anzahl	%
I—II	44	52	82	39	126	43
III—IV	41	48	127	61	168	57
	85	100	209	100	294	100
Sozialgruppe unsicher	—		1		1	
	85		210		295	

[illegible] des Materials nach Sozialgruppe und Heredität.

Tabelle 13

	Männer	%	Frauen	%	Total	%
Verstorbene	103	28	70	34	173	30
Überlebende	259	72	137	66	396	70
	362	100	207	100	569	100

Mortalität und Geschlecht.

Männer und Frauen dieses Materials haben, wie die Tabelle zeigt, ungefähr die gleichen Möglichkeiten, den Infarkt zu überleben denn der statistische Test ergab keine nennenswerten Unterschiede.

Der Zusammenhang von Alter und Mortalität ist von Tabelle 14 erfasst.

Tabelle 14

Alter	Männer Alle	Männer Verstorbene	Männer Verstorbene in %	Frauen Alle	Frauen Verstorbene	Frauen Verstorbene in %	Alle Alle	Alle Verstorbene	Alle Verstorbene in %
unter 40	10	1	1	2	—	0	12	1	8
40—50	60	13	22	24	4	17	84	17	20
50—60	138	31	22	35	8	23	173	39	23
60—70	117	38	32	83	27	33	200	65	32
70 und mehr	37	20	54	63	31	49	100	51	51
	362	103	28	207	70	34	569	173	30

Mortalität in verschiedenen Altersgruppen.

Wie die Tabelle zeigt, nimmt die Mortalität mit dem Alter zu.

Zusammenfassend kann man feststellen, dass das Material eine klare männliche Dominanz zeigt, dass jedoch in der Gruppe der mehr als 70-jährigen weibliche Dominanz vorliegt. Beim Vergleich der beiden Beobachtungsperioden ergab sich eine ungefähr unveränderte Verteilung der Geschlechter. Die Erkrankung trat am häufigsten bei Männern zwischen 50—60 J. und bei Frauen von 60—70 J. auf. Eine gewisse Tendenz in der Richtung dass die Zahl der Patienten unter 50 J. im Verhältnis zum Gesamtmaterial während der Beobachtungszeit etwas zugenommen hat, ist erkennbar. Für Beobachtungsperiode II ergibt sich demgegenüber eine überaus deutliche Zunahme der Altersgruppe 70 J. und darüber. Diese Vermehrung ist statistisch signifikant; eine entsprechende Zunahme alter Personen der Bevölkerung von Helsinki liegt nicht vor. Bei der Mortalität tritt keine Dominanz der Männer (oder Frauen) auf die Möglichkeiten des Überlebens verteilen sich ungefähr gleich. Was das Verhältnis von Lebensalter und Mortalität betrifft, ist mit steigendem Alter eine klare Mortalitätszunahme festzustellen.

Infarkte auf in der Verwandtschaft von Männern, die sich zu Sozialgruppe I—II zählten als bei denen, die zu Gruppe III—IV gehörten während ein umgekehrtes Verhältnis bei den Frauen zu herrschen schien. Das letzt erwähnte Resultat erwies sich jedoch beim statistischen Test nicht als di rekt signifikant. Ein Vergleich der beiden Beobachtungsperioden ergab eine höhere hereditäre Belastung bei den Patienten der früheren Periode Dieses Ergebnis war statistisch bei nahe signifikant.

Frühere Stenokardie

Es ist häufig die Meinung zu hören dass Herzinfarkte ohne jede Vorwar nung, "wie der Blitz aus heiterem Himmel" kommen. Wahrscheinlich hat der dramatische Verlauf der Er krankung zu dieser allgemeinen Vor stellung beigetragen. Die Durchsicht der Literatur ergibt demgegenüber — wie oben ersichtlich — dass eine grosse Anzahl von Autoren bei mehr als 50 % ihrer Patienten vor dem Auftreten der Coronarthrombose stenokardische Beschwerden feststel len konnte

Tabelle 29 gibt an, in welchem Um fang bei den Patienten des Materials früher Stenokardie aufgetreten war Gemeint ist hierbei nicht eine Stenokardie die der Patient ein paar Tage oder Wochen vor dem Ausbruch der Erkrankung gemerkt hatte sondern eine Stenokardie die den Patienten in seinem täglichen Leben überhaupt entschieden gestört hatte

Tabelle 29

	Männer	%	Frauen	%	Alle	%
Frühere Stenokardie	223	67	119	65	342	66
Ohne frühere Stenokardie	111	33	65	35	176	34
Unsicher					51	

Auftreten früherer Stenokardie bei den Patienten des Materials

Wie die Tabelle zeigt, hatten 66 % der Patienten des vorliegenden Materials schon früher an Stenokardie gelitten.

Tabelle 30 zeigt Beobachtungen der Wirkung früherer Stenokardie auf den Verlauf der Krankheit. Die Ta belle wurde errechnet aus einem Vergleich der Mortalität solcher Pa tienten, die früher stenokardische Beschwerden gehabt bzw nicht gehabt hatten. 51 unsichere Fälle wur den bei Aufstellung der Tabelle weggelassen.

Tabelle 30

	Alle	Verstor ben	Verstor bene %
frühere Stenokardie	342	97	28
ohne frühere Stenokardie	176	45	26

Die Mortalität der Patienten mit bzw ohne Stenokardie.

Auf Grund der Tabelle lässt sich ein direkter Unterschied in der Mortalität von Patienten die früher Stenokardie gehabt hatten und anderen nicht erkennen Bedauerlicherweise bilden die 51 Patienten die auf Grund unvollständiger Angaben ausgeschlos-



Darstellung des Untersuchungs-Materials nach dem Erkrankungsmonat (theoretische Monatswert = 100)

Tabelle 18

Erkrankungsmonat	1945—48 %		1949—52 %	
1	7		8	
2	4		7	
3	7	18	7	22
4	8		6	
5	10		10	
6	7	25	6	22
7	5		7	
8	5		7	
9	13	23	7	21
10	12		11	
11	11		11	
12	11	34	13	35
	100		100	

Prozentuale Aufgliederung des periodisierten Materials nach Monaten

Hinsichtlich der Herzinfarktfrequenz während der einzelnen Jahreszeiten zeigt das Material eine deutliche Zunahme während der Monate Mai Oktober—Dezember Beim statistischem Test erwies sich diese Zunahme als signifikant.

In diesem Zusammenhang wurde auch die Tageszeit zu der der Infarkt auftrat, beachtet. Leider war allerdings mehr als die Hälfte der Krankengeschichten in diesem Punkt unvollständig, weshalb 286 Fälle aus dem Material ausgeschlossen wurden Hierdurch hat die statistische Zuverlässigkeit natürlich gelitten.

Das reduzierte Material wurde in die aus Tabelle 17 ersichtlichen 5 Gruppen eingeteilt. Da die Stundenzahl innerhalb der Gruppen verschieden ist erhellt aus den Frequenz bzw Prozentzahlen nicht die wirkliche Bedeutung der jeweiligen Gruppe Es wurde deshalb in die Tabelle ein theoretischer Wert aufgenommen, der angibt, wie das Material bei einer gleichmässigen Verteilung auf die 24 Stunden des Tages ausgesehen hätte. Bei Beachtung des Unterschiedes zwischen dem empirischen und dem theoretischen Wert kann man feststellen, ob sich die Frequenz auf eine bestimmte Tageszeit konzentriert.

Rückfallinfarkte

Die Frequenz der Rückfallinfarkte die von den Autoren des angeführten Schrifttums beobachtet worden ist, zeigt sehr starke Schwankungen. Es scheint deshalb angezeigt, die Frequenz der Rückfallinfarktfälle im vor liegenden Material aufmerksam zu untersuchen. Bei den 569 Infarktfäl len des vorliegenden Materials traten 88 Rückfallinfarkte auf 15 der Fälle hatten 3 oder mehr Infarkte gehabt, 61 der Fälle waren nicht mit Sicherheit zu klären und wurden ausgeschlossen. Tabelle 33 gibt die Frequenz der Rückfallinfarkte im vor liegenden Material und die Verteilung der Rückfälle bei den Geschlechtern an.

Tabelle 33

	Männer	%	Frauen	%	Total	%
Rückfallinfarkt	59	18	29	16	88	17
Erstinfarkt	266	82	154	84	420	83
	325	100	183	100	508	100
unsicher	37		24		61	
	362		207		569	

Frequenz der Rückfallinfarkte und deren Verteilung auf die Geschlechter

Die Tabelle zeigt, dass sich die Rückfallinfarkte auf 17 % des vorliegenden Materials belaufen. Die Ver teilung der Rückfälle nach Geschlechtern zeigt etwa dasselbe Verhältnis wie die der Erstinfarkte

Was die Prognose betrifft, so kann es aufschlussreich sein, die Überlebensaussichten der Rückfallpatienten des vorliegenden Materials zu beobachten und sie mit denen der Erstin farktpatienten zu vergleichen Die bisherigen Forschungen zu dieser Frage haben, wie die herangezogene Literatur gezeigt hat widersprechen de Ergebnisse gezeitigt. Die zu diesem Zweck aufgestellte Tabelle 34 zeigt, dass sich bei den Rückfallpatienten eine leichte Tendenz zu erhöhter Mor talität beobachten lässt. Statistisch signifikant war diese Tendenz jedoch nicht.

Tabelle 34

	Männer			Frauen			Total		
	alle	verst.	%	alle	verst.	%	alle	verst.	%
Rückfallinfarkt	59	17	29	29	10	34	88	27	31
Erstinfarkt	266	68	26	154	44	29	420	112	27
unsicher							61		
							569		

D[illegible] Mortal[illegible] bei R[illegible]kfalli[illegible]f[illegible]kten

prozentuale Verteilung war in dieser Hinsicht in Periode I und Periode II gleich. Was die Tageszeit der Erkrankung betrifft, so ist eine erhöhte Frequenz während der Morgenstunden, 6—9 Uhr und der Nachmittagsstunden, 12—16 Uhr festzustellen.

Sozialgruppen

Es wurde für angezeigt gehalten, auch die soziale Gruppierung in der Untersuchung zu berühren, nachdem der Herzinfarkt allgemein für eine Krankheit der besitzenden Klassen angesehen und sogar "Managerkrankheit" genannt worden ist. Das Material wurde zu diesem Zweck nach einem System untergliedert, das auch von der statistischen Abteilung des finnischen Bevölkerungsverbandes e.V verwendet wird.

Sozialgruppe I Vollakademiker Freie Berufe leitende Persönlichkeiten sowie Personen in entspr sozialer Stellung.

Sozialgruppe II Arbeitsleiter technische Angestellte selbständige Kleinunternehmer und Handwerker Büroangestellte mit selbständiger Arbeit sowie Personen in entspr sozialer Stellung

Sozialgruppe III Andere Büroangestellte, Facharbeiter mit wenigstens zweijähriger Ausbildung Verkäufer Kellner u. Bedienungen sowie Personen in entspr sozialer Stellung

Sozialgruppe IV Gelegenheitsarbeiter Hilfskräfte Aufwartungen, Hausangestellte sowie Personen in entspr sozialer Stellung

Tabelle 19 ist nach dieser Gruppierung ausgearbeitet und gibt ausserdem Aufschluss über den Anteil der betr Sozialgruppen an der Gesamtbevölkerung von Helsinki.

Tabelle 19

Sozialgruppe	Männer		Frauen		Alle		Bevölkerung von Helsinki 1.J 1950
		%		%		%	%
I	67	18	32	16	99	18	12
II	93	26	36	18	129	23	21
III	144	40	75	39	219	39	41
IV	57	16	52	27	109	20	26
	361	100	195	100	556	100	100
unbekannt	1		12		13		
	362		207		569		

Aufgliederung des Material nach Sozialgruppe und Geschlecht

Die Tabelle zeigt dass in Gruppe I mehr Infarktfälle auftraten als es nach deren Anteil an der Bevölkerung in Helsinki zu erwarten gewesen

Herangezogen wurden nach willkürlicher Wahl 150 Patienten der inner medizinischen Abteilungen des Maria Krankenhauses die während der Jahre 1945—1952 aufgenommen waren (nicht wegen Herzinfarkt) Die Altersgruppen des Kontrollmaterials entsprachen im grossen ganzen denen des Untersuchungsmaterials

Tabelle 37 verzeichnet das Kontrollmaterial in derselben Weise wie Tab 36 das Infarktmaterial welches aus 120 Männern und 30 Frauen bestand.

Tabelle 37

	Männer	%	Frauen	%	alle	%
erhöhter Blutdruck	33	27,5	22	73,3	55	36 7
nicht „	97	72,5	6	26 7	95	63,3
	120	100	30	100	150	100

A ftreten on erhöhtem Blutdruck bei den Patienten eines Kontrollmaterials

Ein Vergleich von *Tabelle 36* und Tabelle 37 ergibt, dass im Kontrollmaterial ebensoviel erhöhter Blutdruck wie im Beobachtungsmaterial auftrat und dass auch im Kontrollmaterial überwiegend bei den Frauen erhohter Blutdruck vorkam Hier aufhin wurde noch einmal der Blutdruck von 100 willkürlich gewählten Frauen zum Vergleich herangezogen wobei sich ein erhöhter *Blutdruck* in 44 % der Fälle ergab

Es dürfte nicht uninteressant sein zu untersuchen, inwieweit sich die Überlebensaussichten derjenigen Patienten die erhöhten Blutdruck hatten von denen ohne erhöhten Blutdruck unterscheiden. Zu diesem Zweck wurde Tabelle 38 aufgestellt.

Tabelle 38

	Männer			Fra en			Alle		
	Summe	erst.	verst.%	Summ	verst.	verst.%	Summe	verst.	verst.%
erhöhter Blutdruck	98	28	27	101	30	29	199	58	29
nicht „	237	57	24	89	23	26	326	80	25
unsicher	27			17			44		
							569		

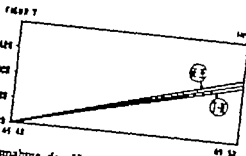
Ie Mortalität bei Patienten mit bzw ohn erhöhten Blutdruck.

Wie die Tabelle angibt, war die Mortalität bei beiden Infarktpatiengruppen ungefähr gleich gross Auch beim statistischen Test konnte ein erweisliches Unterschied nicht festgestellt werden. Auch war kein

Tabelle 21

T eszeit	Sozialgruppe I—II %	III—IV	Differ o
Morgen	27	17	10
Vormittag	10	12	—2
Nachmittag	18	25	—7
Abend	22	23	—1
Nacht	23	23	0
	100	100	0

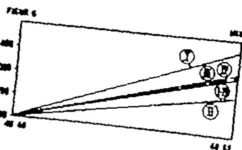
Aufgliederung des Materials nach Sozialgruppen und Erkrankungszeitpunkt.



Zunahme der Herzinfarktpatienten bei ein einen sozialen Gruppen on der Periode 1945—1948 bis zu Periode 1949—195 (Indexba i 1945—1948 = 100)

Die Tabelle ergibt eine erhöhte Frequenz für die Morgenstunden bei den Gruppen I u.II und für die Nachmittagsstunden bei den Gruppen III u.IV Dieses Resultat konnte beim statistischen Test jedoch nicht als signifikant angesehen werden.

Nachdem das Material im Verlauf der Jahre 1945—1952 eine starke Erhöhung der Frequenz von Infarkten zeigt, schien es aufschlussreich zu untersuchen inwieweit diese Zunahme bei einer der Sozialgruppen evtl. höher lag als bei anderen. Zu diesem Zweck wurden Figur 6 und Figur angelegt. Das Material ist in die Perioden 1945—1948 sowie 1949—1952 eingeteilt worden, und ausgehend von den Zahlen für Periode I wurde ein Index mit Basis 100 ausgerechnet.



Nach Figur 6 ist die Zunahme am grössten in Sozialgruppe I und am kleinsten in Sozialgruppe II. Bei der Zusammenlegung von Sozialgruppe I mit II und III mit IV in Figur 7 ist die Zunahme bei den beiden Gruppen ungefähr gleich.

Die Zunahme innerhalb Gruppe I war zwar die grösste doch ist der Unterschied zwischen den Gruppen nicht so gross dass er sich als statistisch signifikant erwiesen hätte

Die Untersuchung der Sozialgruppen zusammenziehend kann man konstatieren, dass die bei den wohlhabenderen Klassen auftretende Herzinfarktfrequenz höher ist.

Ein Blick auf das prozentuale Verhältnis von Männern und Frauen zeigt, dass in Sozialgruppe IV verhältnismässig mehr Frauen vorkommen. Während des Zeitraumes 1945—1952 trat in dem Material eine Zunahme der Herzinfarktfrequenz auf, die bei allen Sozialgruppen ungefähr gleich war ein leichtes Übergewicht zeigt allerdings Sozialgruppe I statistisch signifikant ist dieses jedoch nicht.

so viele kleine Untergruppen ergeben dass eine auch nur annähernd zuverlässige statistische Behandlung des Materials — das ja an sich schon reduziert ist — unmöglich geworden wäre Es wurde deshalb geschieden danach ob der betr Patient Tabak bzw Alkohol zu geniessen pflegte oder nicht.

Tabelle 40 gibt das Verhältnis von Rauchern und Nichtrauchen bei den Patienten an.

Tabelle 40

	Männer	%	Frauen	%	Alle	%
Raucher	206	82	13	22	219	71
Nichtraucher	44	18	47	78	91	29
	250	100	60	100	310	100
ohne Angabe	112		147		259	
Summe	362		207		569	

Der Tabakgenuss der Infarktpatienten.

Wie die Tabelle zeigt, waren 82 % der männl. Patienten und 22 % der weibl Patienten Raucher

Um eine Vorstellung über die Relevanz dieser Zahlen zu erhalten, wurde aus Nichtherzpatienten der inner medizinischen Abteilungen des Maria Krankenhauses während der gleichen Zeit ein Vergleichsmaterial befragt. Das Verhältnis zwischen den beiden Gruppen geht aus Tabelle 41 hervor

Tabelle 41

	Männer	%	Frauen	%	Alle	%
Raucher	76	63	7	23,3	83	55,3
Nichtraucher	44	37	23	76 7	67	44 7
	120	100	30	100	150	100

R ucher und Nichtraucher in einem Kontrollmaterial.

Ein Vergleich von Tabelle 40 und Tabelle 41 ergibt, dass im Infarktmaterial prozentual mehr männliche Raucher auftraten. Das Ergebnis war beim statistischen Test signifikant.

Tabelle 42 beleuchtet das Verhältnis von Mortalität bei Herzinfarkt und Tabakgenuss Da die diesbezüglichen Angaben über die Frauen des Untersuchungsmaterials sehr spärlich sind, wurde diese Gruppe nicht separat untersucht.

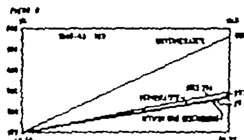
Tabelle 23

	40—49		50—59		60—69		70—	
	Material %	Helsinki %	Material %	Helsinki %	Material %	Helsinki %	Material %	Helsinki %
ledig	[illegible]	10	7	9	7	8	6	8
verh.	85	84	86	83	86	79	71	65
übrige	5	6	7	8	7	13	23	27
	100	100	100	100	100	100	100	100

Die Männer des Materials nach Familienstand und Alter verglichen mit der männl. Gesamtbevölkerung von Helsinki (1950)

Aus der Tabelle ergibt sich, dass bei den Männern der Anteil der Patienten am Material den entspr. Zahlen der männl. Gesamtbevölkerung auch nach dem Familienstand im grossen ganzen entspricht.

Um festzustellen, ob sich der Anteil der unverheirateten Frauen während der späteren Beobachtungsperiode vergrössert hat, wurde Tabelle 24 und im Anschluss daran Figur 9 ausgearbeitet.



Die Frauen des Untersuchungsmaterials, dargestellt nach dem Familienstand während der Perioden 1945—1948 und 1949—1952. (Indexwert für die Periode 1945—1948 = 100)

Tabelle 24

	45—48	49—52	Ind. 45—48 100
ledig	5	28	560
verh.	24	64	267
übrige	23	61	265
	52	153	294
unbekannt	—	2	
	52	155	297

Die Frauen des Materials nach dem Familienstand

Beim Vergleich der früheren und der späteren Beobachtungsperiode lässt sich erkennen, dass der Anteil der unverheirateten Frauen am Material verhältnismässig stärker gestiegen ist als der der anderen Gruppen. Die Gruppen blieben jedoch alle in so engen Grenzen, dass sich beim statistischen Test signifikante Resultate nicht erzielen liessen.

Zusammenfassend kann man feststellen, dass sich bei den verheirateten Frauen des Materials in bedeutend grösserem Umfang Infarktfälle zeigten als es die Zusammensetzung der Gesamtbevölkerung von Helsinki erwarten liesse. Diese Tendenz erlosch mit zunehmendem Alter. Dieses an sich schon deutliche Verhältnis von Familienstand und Infarkt bei Frauen wird noch auffälliger dadurch, dass ein ähnlicher Zusammenhang zwischen Familienstand und

Aus der Tabelle lässt sich ersehen dass 20 % der Männer und 85 % der Frauen abstinent waren.

Um festzustellen, inwieweit das Verhältnis der Abstinenten im Material mit den allgemeinen Verhältnissen übereinstimmt, wurde aus willkürlich gewählten anderen Patienten der innermedizinischen Abteilungen des Maria-Krankenhauses während des gleichen Zeitraumes ein Kontroll material gewählt.

Die Resultate zeigt Tabelle 45

Tabelle 45

	Männer	%	Frauen	%	alle	%
Alkohol +	68	56 7	10	33,3	78	52
Alkohol —	52	43,3	20	66 7	72	48

Alkol olgenuss der Patienten i einem Kontrollmaterial.

Wie aus der Tabelle ersichtlich bezeichnete sich ein überraschend grosser Teil der männlichen Patienten des Kontrollmaterials als abstinent Es könnte dies darauf beruhen dass das Kontrollmaterial aus Krankenhauspatienten bestand die z.T Chroniker waren, und die von ihrem Arzt in früherer Zeit zur Abstinenz aufgefordert worden waren.

Beim Vergleich von Tabelle 44 und Tabelle 45 kann man jedoch konstatieren, dass das Infarktmaterial prozentual weniger abstinente Männer enthält. Für die Männer war dieses Resultat auch beim statistischen Test signifikant, während die entspr Zahlen für die weiblichen Patienten zu klein waren.

Tabelle 46 beleuchtet das Verhältnis von Abstinenz und Herzinfarkt Mortalität. Da die entspr Angaben über die weiblichen Patienten so spärlich waren wurde diese Gruppe nicht separat betrachtet.

Tabelle 46

	Männer				Gesamt Material			
	zusammen	verst	verst %	Median Alter	zusammen	verst.	verst. %	Median Alter
Alkohol +	196	37	19	56	203	40	20	56
Alkohol —	48	17	35	63	98	25	26	63
ohne Angabe	116	49	42		266	108	41	

V hal n on Alk holgen und Mortal t t im vorliegenden Untersuchungsmaterial.

Die Betrachtung der Tabelle ruft den Eindruck hervor dass die Mortalität bei den nicht abstinenten Infarktpati nten geringer sei Beim statistischen Test erwies sich dieses Ergebnis indessen nicht als signifikant. Werden bei dieser Untersuchung jedoch ausschliesslich die männlichen Patienten herangezogen, so wird das Ergebnis auch beim statistischen Test nahezu signifikant.

Wie die Tabelle zeigt, traten bei den zu Sozialgruppen I—II gehörigen Männern in der Verwandtschaft verhältnismässig mehr Infarktfälle auf als bei den Männern der Sozialgruppen III—IV. Zu beachten ist jedoch die Möglichkeit, dass die hereditäre Anamnese bei den Sozialgruppen I—II zuverlässiger ist als die der Sozialgruppen III—IV. Die Resultate waren bei statistischem Test nicht direkt signifikant.

Ein entsprechender Vergleich wurde auch bei den Frauen der verschiedenen Sozialgruppen vorgenommen und in Tabelle 27 ausgewertet.

Tabelle 27

FRAUEN Sozialgruppe	Hereditat + Anzahl	%	Hereditat — Anzahl	%	Gesamt Anzahl	%
I—II	10	29	39	36	49	34
III—IV	24	71	70	64	94	66
	34	100	109	100	143	100
Sozialgruppe unsicher	3		6		9	
	37		115		152	

Die weibl. Patienten des Material nach Sozialgruppe und Heredität.

Im Gegensatz zu den entspr. Ergebnissen bei den Männern zeigt Tabelle 27 bei den zu den Sozialgruppen III—IV gehörenden Frauen ein häufigeres Auftreten von Infarkten in der Verwandtschaft als bei den zu den Sozialgruppen I—II gehörenden Frauen. Leider ist die Anzahl der Fälle nicht gross genug, um als statistisch zuverlässig gelten zu können.

Tabelle 28 bringt eine Zusammenstellung der Infarktfälle in der Verwandtschaft der Patienten des vorliegenden Materials in den Jahren 1945—1948 und 1949—1952.

Die Tabelle ergibt, dass in der früheren Periode mehr hereditär belastete Patienten (35 %) auftraten als in der zweiten Periode (25 %). Dieses Resultat ist statistisch nahezu signifikant.

Tabelle 28

	1945—48	%	1949—52	%	Gesamt	%
Heredität +	36	35	86	25	122	27
Heredität —	67	65	258	75	325	73
Summe	103	100	344	100	447	100
Keine Angaben	28		94		122	
	131		438		569	

Infarktfälle in der Verwandtschaft der Patienten des Materials während der Jahre 1945—1949 u. 1949—1952.

Zusammenfassend kann man feststellen, dass in der Verwandtschaft der Infarktpatienten bedeutend häufiger Infarkte auftraten als bei den Patienten des Kontrollmaterials.

Verhältnismässig häufiger traten

abschnitte soll weiter unten etwas genauer dargestellt werden

Zu Ende des Krieges — Spätherbst 1944 — und im anschliessenden Jahr 1945 herrschte in Helsinki nahezu Hungersnot Sämtliche Nahrungsmittel waren rationiert, die Zuteilungen waren minimal und konnten nicht einmal immer ausgegeben werden. Kartoffeln waren Mangelware man a..s Kohl und Steckrüben. Brot schlangen gehörten zum normalen Strassenbild Weissbrot existierte nicht. Die Butterration belief sich zeitweise auf 150 gr pro Monat für die Butter wurden auf dem schwarzen Markt bis zum 15-fachen des amt lichen Preises nämlich bis 2000 — Fmk bezahlt, während der Mittelpreis nach dem Ausklingen der Inflation im Jahre 1952 rd. 450 Fmk betrug. Sahne war nicht erhältlich selbst Milch konnte zeitweise nur an Kin der ausgegeben werden. Wer beim Fleischer einen Perdekopf ergatterte und sich damit eine Suppe zurichten konnte durfte von Glück sagen. Die Restaurants führten "Wildragoûts" zweifelhafter Provenienz, meist aus Tauben Fuchs- Kaninchen- und Pferdefleish. Bei Einladungen war das Beste was man anbieten konnte ein aus "hintenherum" gekauften Zutaten bereiteter Crèmekuchen. Wer einen schwarzen Schinken er wischen konnte wollte ihn so fett wie möglich haben — auch hierfür waren die Preise natürlich enorm.

Allmählich wurde dann die Ver sorgungslage besser im Jahr 1947 wurden die Rationen erhöht am 10 IX 1947 wurde die Fleischbewirtschaftung aufgehoben. Im Jahre 1949 wurden sodann Butter Schmalz, Milch und Käse kartenfrei. Die Er nährung die seit Kriegsende haupt sächlich aus Kohlehydraten bestan den hatte begann nun reichlich Proteine und Fette zu enthalten. Die Gewichtzunahme der Bevölkerung von Helsinki war augenscheinlich Verf. kam von 58 kg im Jahre 1946 auf 89 kg im Jahre 1950 Es ist garnicht zu bezweifeln, dass in der Versorgungslage von Helsinki innerhalb des Zeit raums der vorliegenden Unter suchung eine durchgreifende Verän derung stattgefunden hat. Hatte die Bevölkerung jahrelang nur das Alleräusserste zum Leben bekommen kön nen, so schlugen die Verhältnisse nun in das andere Extrem um man überass sich förmlich an Proteinen und Fett.

Eine genauere Vorstellung der Versorgungslage von Helsinki geben die nachfolgenden Tabellen. Tabelle 48 zeigt die Zahlen des Fleischverkaufs in Helsinki in den Jahren 1945 —1952 die Angaben stammen vom städt. Schlachthaus.

Tabelle 48

Jahr	Fleischverkauf (per kg)	
1945	2.925 000	
1946	2.603 000	
1947	11 142.000	Fleischbewirt
1948	11 706.000	schaftung auf
1949	16.500 000	gehoben 1947
1950	15.840.000	
1951	16 173.000	
19.,2	17.317.000	

De Flei ch erkauf in H lunki nach A gaben d s städt Schlacht ha se

sen werden mussten, ein Unsicherheitsmoment da 31 dieser Patienten verstarben und somit in einem gewissem Umfang die Mortalitätsziffer erhöhen.

Zur weiteren Beleuchtung dieser Frage wurde sodann auch Tabelle 31 ausgearbeitet, in der die Patienten mit früheren stenokardischen Beschwerden nach den Zeiträumen 1945—1948 und 1949—1952 aufgegliedert wurden, nachdem die Mortalität in diesen Perioden sehr verschieden war (siehe auch Tab 5)

Tabelle 31

	1945—48	%	1949—52	%	Alle	%
Überlebende	46	54	199	78	245	72
Verstorbene	39	46	58	22	97	28
Summe	85	100	257	100	342	100

Die Mortalität der Patienten mit früherer Stenokardi während der Perioden 1945—1948 und 1949—1952

Der Mortalitätsprozentsatz von Patienten, die früher an stenokardischen Beschwerden gelitten hatten, war während der Periode 1945—1948 wie die Tabelle zeigt 46 %. Das ist, wie aus Tabelle 5 hervorgeht derselbe Prozentsatz wie für das Gesamtmaterial während dieser Periode. Auch der Mortalitätssatz von 22 % der sich entsprechend für die zweite Periode ergibt, ist ungefähr genau so gross wie der des Gesamtmaterials während dieser Periode der sich auf 26 % beläuft. Hieraus kann geschlossen werden dass im vorliegenden Material die Mortalität der Patienten, die früher stenokardische Beschwerden hatten ungefähr mit der Mortalität der übrigen Patienten übereinstimmt.

Um eine Vorstellung zu gewinnen, inwieweit die Stenokardie mit dem Ansteigen der Infarktfälle während der Beobachtungszeit Schritt gehalten hat, wurde Tabelle 32 errechnet. 51 unsichere Fälle mussten hierbei ausscheiden.

Tabelle 32

	1945—48	%	1949—52	%	Alle	%
frühere Stenokardie	85	70	237	65	342	66
ohne frühere Stenokardie	36	30	140	35	176	34

Da Auftreten frühere Stenokardie bei den Infarktpatienten während der Perioden 1945—1948 und 1949—1952.

Wie die Tabelle zeigt, war in beiden Perioden die Zahl der Patienten, bei denen vor Auftreten des Infarkts stenokardische Beschwerden vorgekommen waren, etwa gleich gross.

Zusammenfassend kann man feststellen, dass 66 % der Patienten des Materials vor der Erkrankung an Coronarthrombose schon stenokardische Beschwerden gehabt hatten. Die Mortalität der Patienten mit früherer Stenokardie war nicht grösser als die durchschnittliche Mortalität dieses Materials. Während beider Beobachtungsperioden traten in ungefähr gleichem Umfang Patienten auf, die schon früher stenokardische Beschwerden gehabt hatten.

abschnitte soll weiter unten etwas genauer dargestellt werden

Zu Ende des Krieges — Spätherbst 1944 — und im anschliessenden Jahr 1945 herrschte in Helsinki nahezu Hungersnot. Sämtliche Nahrungs mittel waren rationiert, die Zuteilungen waren minimal und konnten nicht einmal immer ausgegeben werden. Kartoffeln waren Mangelware, man ass Kohl und Steckrüben. Brot schlangen gehörten zum normalen Strassenbild. Weissbrot existierte nicht. Die Butterration belief sich *zeitweise auf 150 gr pro Monat für* die Butter wurden auf dem schwarzen Markt bis zum 15-fachen des amtlichen Preises nämlich bis 2000 — Fmk bezahlt während der Mittelpreis nach dem Ausklingen der Inflation im Jahre 1952 rd. 450 Fmk betrug Sahne war nicht erhältlich, selbst Milch konnte zeitweise nur an Kin der ausgegeben werden Wer beim Fleischer einen Perdekopf ergatterte und sich damit eine Suppe zurichten konnte, durfte von Glück sagen. Die Restaurants führten "Wildragoûts" zweifelhafter Provenienz, meist aus Tauben- Fuchs- Kaninchen und Pferdefleish. Bei Einladungen war das Beste was man anbieten konnte ein aus "hintenherum" gekauften Zu taten bereiteter Crèmekuchen. Wer einen schwarzen" Schinken er wischen konnte wollte ihn so fett wie möglich haben — auch hierfür waren die Preise natürlich enorm.

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Eine genauere Vorstellung der Versorgungslage von Helsinki geben die nachfolgenden Tabellen. Tabelle 48 zeigt die Zahlen des Fleischver kaufs in Helsinki in den Jahren 1945 —1952 die Angaben stammen vom städt. Schlachthaus.

Tabelle 48

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1945	2.925 000	
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1949	16.500 000	gehoben 1947
1950	15.840 000	
1951	16.173 000	
1952	17.317.000	

Der Fleischverkauf in Helsinki nach Angaben des städt. Schlachthauses

Es dürfte nicht uninteressant sein festzustellen inwieweit während der Beobachtungsperiode II eine erhöhte Anzahl von Rückfallinfarkten aufgetreten war. Zur Klärung dieser Frage wurde Tabelle 35 aufgestellt.

Tabelle 35

	Sämtl. Fäll	Rückfall Infarkte	%
1945—48	117	15	13
1949—52	391	73	19
unsicher	61		
	569		

Rückfallinfarkte in periodenweiser Gliederung.

Wie die Tabelle zeigt, bestand während der Periode II eine leichte Tendenz zu erhöhten Rückfallzahlen, jedoch war das Ergebnis statistisch nicht signifikant.

Zusammenfassend darf gesagt werden, dass die Rückfallinfarkte 17 % des gesamten Materials bildeten. Die Häufigkeit der Rückfallinfarkte bei Frauen und bei Männern war ungefähr die gleiche wie bei Patienten mit Erstinfarkt.

Hypertonie

Wie aus der Literaturübersicht hervorging ist eine beträchtliche Anzahl der Forscher der Ansicht, dass bei Patienten mit Coronarleiden hoher Blutdruck sehr häufig ist, und zwar ganz besonders bei Frauen. Um darzulegen, in welchem Umfang dies auch für das vorliegende Material gilt, wurde Tabelle 36 aufgestellt. Als Grenzwert wurde ein systolischer Druck von 160 mmHg angesetzt — ein Wert, den die meisten der zitierten Autoren gewählt hatten. In 44 Fällen waren hinsichtlich des Blutdrucks genaue Angaben nicht erhältlich.

Tabelle 36

	Männer	%	Frauen	%	Alle	%
erhöhter Blutdruck	98	29	101	72	199	38
nicht erhöhter Blutdruck	237	71	89	28	326	62
	335	100	190	100	525	100
unsicher	27		17		44	
	362		207		569	

Auftreten von erhöhtem Blutdruck bei den Herzinfarktfällen.

Die Tabelle zeigt, dass bei 38 % der Herzinfarktfälle des Materials erhöhter Blutdruck vorkam. Die weiblichen Patienten zeigten mit 72 % einen ganz besonders hohen Anteil.

Um Aufschluss darüber zu erlangen, ob das Vorkommen von erhöhtem Blutdruck im vorliegenden Material besonders markant ist, wurde ein Vergleichsmaterial ausgearbeitet.

Zusammenfassend ist festzustellen, dass die Herzinfarktfrequenz des vorliegenden Materials parallel zu dem steigenden Butter und Fleischverbrauch in Helsinki verläuft beim Zuckerverbrauch herrscht nicht die gleiche Tendenz. Der Lebensstandard stieg gleichzeitig beträchtlich.

Unterschied zwischen der Mortalität von Männern und Frauen mit erhöhtem Blutdruck zu eruieren. Tabelle 39 gibt eine Übersicht über das Auftreten von erhöhtem Blutdruck in den einzelnen Perioden der Untersuchung

Tabelle 39

	1945—48	%	1949—5	%	1945—52	%
erhöhter Blutdruck	46	39	153	38	199	38
nicht „	72	61	254	62	326	62
zusammen	118	100	407	100	525	100
unsicher	13		31		44	
	131		438		569	

Auftreten von erhöhtem Blutdruck bei den Infarktpatienten während der beiden Beobachtungsperioden

Ein Unterschied im Auftreten von erhöhtem Blutdruck zwischen den beiden Beobachtungsperioden konnte, wie die Tabelle zeigt nicht festgestellt werden.

Zusammenfassend lässt sich sagen, dass in 38 % der Fälle des vorliegenden Materials erhöhter Blutdruck vorlag. Der Satz der Frauen lag bei 72 %. In zwei Kontrollgruppen von etwa gleichaltrigen Nicht Infarktpatienten trat auch in grossem Umfang Hypertonie auf. Die Mortalität der beiden Patientengruppen — mit bzw ohne erhöhten Blutdruck — war etwa gleich. Eine gewisse Beachtung verdient der Umstand, dass die Mortalität der Männer und Frauen etwa gleich war obwohl erhöhter Blutdruck bei 72 % der Frauen, aber nur bei 20 % der Männer des Materials festgestellt wurde. Dieses Ergebnis legt den Schluss nahe dass erhöhter Blutdruck im vorliegenden Material auf die Überlebensaussichten der Infarktpatienten ohne Einfluss ist. Das Auftreten von erhöhtem Blutdruck war während beider Beobachtungsperioden gleich.

Tabak und Alkohol

Es wurde in vorliegendem Material auch der Versuch unternommen zu klären, inwieweit Tabak und Alkohol in Bezug auf den Herzinfarkt eine Rolle spielen. Da die Angaben den Krankenhausjournalen entnommen sind, welche in dieser Beziehung nicht immer vollständig waren musste die Untersuchung leider mangelhaft bleiben. Besonders wichtig in einer Untersuchung wie der vorliegenden wäre es gewesen festzustellen, in welchem Umfang der betr Patient Tabak bzw Alkohol genossen hat. Es hätten sich hierdurch dann allerdings

gangen. Ich möchte dies so verstanden wissen, dass gegen Ende der Beobachtungszeit die Zunahme im vorliegenden Material zu einem grossen Teil darauf beruht dass auch leichtere Fälle zur Behandlung und damit auch in die Statistik kamen. Hierzu wäre zu bemerken, dass die diagnostischen und therapeutischen Methoden gegen Ende der Beobachtungszeit besser wurden. Hier ist allerdings mit Vorsicht zu plädieren, denn als Abschlussjahr der Untersuchung wurde das Jahr 1952 gewählt. Das ist kein Zufall. Dieses Jahr wurde herangezogen, *weil erst 1952 die Antikoagulantien-Behandlung* im Maria-Krankenhaus als Routinebehandlung eingeführt und weil erst 1953 die unipolare EKG-Diagnose in Gebrauch genommen wurde Die Verteilung der Infarktfälle auf die Geschlechter hat während des Beobachtungszeitraumes kaum Veränderungen erfahren. Es dürfte immerhin nicht uninteressant sein, festzustellen, dass die männliche Dominanz im vorliegenden Material nicht so ausgeprägt war wie bei den meisten anderen Forschern. Bei der Altersgruppe über 70 J zeigte sich eine weibliche Dominanz, was mit den Ergebnissen einer Reihe anderer skandinavischer Forscher übereinstimmt (44 48 75 81 151)

Was die Alterszusammensetzung im vorliegenden Material betrifft, so entsprach sie im grossen ganzen der Auffassung zu der die meisten anderen Forscher gekommen sind nämlich dass das häufigste Erkrankungsalter bei Männern zwischen 50—60 Jahren, bei Frauen zwischen 60—70 Jahren liegt. Es muss indessen als interessant bezeichnet werden, dass im vorliegenden Material das ja eine deutliche Frequenzzunahme zeigt, während der zweiten Hälfte der Beobachtungszeit eine statistisch signifikante Zunahme der Patienten von mehr als 70 Jahren festzustellen war Dieser Umstand beruht, wie kontrolliert wurde, nicht auf einer entsprechenden Zunahme der betr Altersgruppe der Bevölkerung von Helsinki. Es lässt sich wohl nur konstatieren, dass eine Reihe alter Menschen, die der Erkrankung während *der Hungerjahre entgangen waren*, nun plötzlich vom Herzinfarkt betroffen wurden. Ähnliche Beobachtungen haben Henschen (71) und Gordin (58) gemacht. Zum Teil beruht die Frequenzzunahme im vorliegenden Material demnach darauf, dass gegen Ende der Beobachtungszeit bedeutend mehr alte Personen vom Herzinfarkt betroffen wurden.

Hinsichtlich der Jahreszeit der Erkrankung lässt sich aus dem vorliegenden Material eine deutliche Häufung in den Monaten Mai Oktober November und Dezember erkennen. Die gleiche Frequenzzunahme war sowohl in der ersten wie in der zweiten Hälfte der Beobachtungszeit festzustellen. Die Ursachen für eine derartige Häufung in den genannten Monaten sind schwer zu erklären. Man könnte sich z.B denken, dass ein diätärer Übergang eintritt — die Herbstmonate bringen das Ende der Sommerdiät mit Fisch, Gemüse etc. und führen die Winterdiät heran, bei der mehr animalische Nahrungsmittel

Tabelle 42

	Männer			Gesamtes Material		
	zusammen	verst.	verst. %	zusammen	verst.	verst. %
Raucher	206	47	23	219	49	22
Nichtraucher	44	11	25	91	18	20
ohne Angabe	112	45	40	259	106	41
Summe	362	103		569	173	

Verhältnis von Tabakgenuss und Mortalität im Untersuchungsmaterial.

Wie die Tabelle zeigt, konnte ein statistisch nachweisbarer Unterschied der Mortalität von Rauchern und Nichtrauchern des vorliegenden Materials nicht festgestellt werden. Ein Unsicherheitsfaktor ist die ziemlich grosse Gruppe von Patienten, über die keine Angaben vorliegen.

Um klarzustellen, inwieweit sich die beiden Untersuchungsperioden bezüglich des Tabakgenusses unterschieden, wurde Tabelle 43 ausgearbeitet.

Tabelle 43

	1945—48	%	1949—52	%	1945—52	%
Raucher	36	73	184	70	220	71
Nichtraucher	13	27	77	30	90	29
zusammen	49	100	261	100	310	100
ohne Angabe	82		177		259	
insgesamt	131		438		569	

Verhältnis Raucher : Nichtraucher während der beiden Beobachtungsperioden.

Wie die Tabelle zeigt, war das Verhältnis Raucher : Nichtraucher während beider Beobachtungsperioden gleich.

Tabelle 44 beleuchtet die Frage des Alkoholgenusses bei den Patienten des Materials.

Tabelle 44

	Männer	%	Frauen	%	alle	%
Alkohol +	196	80	9	15	205	68
Alkohol —	48	20	50	85	98	32
	244	100	59	100	303	100
ohne Angabe	118		148		266	
	362		207		569	

Alkoholgenuss der Patienten des Untersuchungsmaterials.

Patienten nach Familienstand und Alter unterschieden worden ferner wurde untersucht in welchem Verhältnis die hier verzeichneten unverheirateten und verheirateten Frauen sowie Witwen und Geschiedene zu den entspr Gruppen der Bevölkerung von Helsinki stehen. Es zeigte sich hierbei, dass das Infarktmaterial bedeutend weniger unverheiratete und bedeutend mehr verheiratete Frauen enthält, als es der Anteil dieser Gruppen an der Bevölkerung von Helsinki voraussetzte. Diese Feststellung bezieht sich auf die jüngeren Jahrgänge während bei den Altersklassen von 70 J und darüber kein Unterschied mehr feststellbar war Bei einer entsprechenden Untersuchung der männlichen Patienten des Materials zeigte sich, dass eine derartige Beobachtung nicht gemacht werden konnte. Es fielen die Zahlen vielmehr im grossen ganzen mit den Zahlen der betr Bevölkerungsgruppe zusammen. Was schützt nun die jüngeren unverheirateten Frauen vor dem Herzinfarkt? Keys (85) war der Ansicht, dass die relative Herzinfarkt Immunität von Frauen jüngerer Jahrgänge hormonale Grundlagen hatte. Vielleicht ist dies auch die Erklärung für die relative Immunität der jüngeren unverheirateten Frauen des Materials gegenüber den verheirateten. Werden die beiden Hälften der Beobachtungsperiode miteinander verglichen, so zeigt sich, dass der Anteil der unverheirateten Frauen in der zweiten Hälfte stärker zugenommen hat als der der verheirateten. Leider erwies sich das Resultat wegen der kleinen Anzahl der Fälle statistisch nicht als signifikant, weshalb hier keine Rückschlüsse gezogen werden können.

Dem hereditären Faktor wird beim Auftreten von Herzinfarkt erhebliche Bedeutung beigemessen. Im Material von Bor (22) hatten 70 % der Herzinfarktfälle eine hereditäre Belastung durch Herz und Kreislaufleiden, während andere Autoren (11 29 141 152) auf 40—50 % gekommen waren. In das vorliegende Material wurden als hereditär belastete Fälle nur solche aufgenommen, deren Geschwister oder Eltern Herzinfarkte hatten. Hiernach ergab sich eine hereditäre Belastung in 25 % der Fälle gegenüber 12,5 % in einem Kontrollmaterial. Nicht unbedeutend erscheint der Umstand, dass während der ersten Hälfte der Beobachtungsperiode — auch statistisch fast signifikant — mehr Patienten mit Infarkten in der Verwandtschaft auftraten als in der zweiten Hälfte. Es erhebt sich somit die Frage ob in Zusammenhang mit der starken Frequenzzunahme während der zweiten Hälfte der Beobachtungszeit andere Faktoren im Entstehungsmechanismus des Herzinfarkts — wie etwa die veränderten Lebensverhältnisse — eine grössere Rolle gespielt haben. Oder könnte der Umstand darauf beruhen, dass in der früheren Periode mehr schwere Fälle mit grösserer hereditärer Belastung aufgetreten waren?

Die Frage inwieweit die Infarktpatienten früher an stenokardischen Beschwerden gelitten hatten oder ob der Infarkt völlig überraschend aufgetreten war hat das Interesse ver

Wie die Tabelle zeigt, lag das Durchschnittsalter der abstinenten Patienten höher als das der nicht-abstinenten. Da die Mortalität bei jüngeren Patienten im allgemeinen niedriger ist als bei den älteren lässt sich die Ursache der niedrigeren Mortalität der nicht abstinenten Patienten somit teilweise mit dem Lebensalter dieser Patienten erklären.

Um klarzustellen, ob während einer der Beobachtungsperioden die Anzahl der nicht abstinenten Infarktpatienten grösser war wurde Tabelle 47 aufgestellt.

Tabelle 47

	1945—48	%	1949—52	%	1945—52	%
Alkohol +	37	72	168	67	205	68
Alkohol —	14	28	84	33	98	32
zusammen	51	100	252	100	303	100
ohne Angabe	80		186		266	

Alkoholgenuss der Infarktpatienten während der Periode 1945—1948 und 1949—1952

Der Alkoholgenuss hat sich während der beiden Beobachtungsperioden bei den Infarktpatienten nicht verändert, wie die Tabelle zeigt.

Zusammenfassend kann man feststellen, dass prozentual mehr Patienten des Infarktmaterials rauchten und nicht abstinent waren als die Personen des Kontrollmaterials.

Hinsichtlich der Mortalität liess sich im vorliegenden Material zwischen Rauchern und Nichtrauchern ein Unterschied nicht feststellen. Was den Zusammenhang von Mortalität und Alkoholgenuss betrifft, so liess sich zwischen den nicht abstinenten männlichen Patienten des Materials eine etwas niedrigere Mortalität konstatieren. Das Durchschnittsalter dieser Patienten war indessen niedriger als das der abstinenten. Rückschlüsse auf das Verhältnis der Geschlechter konnten wegen der geringen Anzahl weiblicher Fälle nicht gezogen werden. Der Tabak und Alkoholgenuss war während der beiden Perioden bei den Infarktpatienten des Materials ungefähr gleich gewesen.

Die Versorgungslage und der Lebensstandard in Helsinki während der Jahre 1945—1952

Wie der Überblick über das Schrifttum zeigte, geht sowohl die Arteriosklerose wie die Herzinfarktanfälligkeit in Hungerzeiten zurück. Das Material vorliegender Untersuchung stammt aus einer Periode die durch den Wechsel von äusserst knapper Lebensmittelversorgung mit rigoroser Bewirtschaftung und nachfolgend völlig unbeschränktem, reichlichem Angebot gekennzeichnet ist. Nur selten dürfte Gelegenheit zur Beobachtung eines so radikalen Umschwungs der Versorgungslage bestehen. Die Ernährungslage während dieser Zeit

schnittsalter der weibl. Patienten höher war. Bei einem Kontrollmaterial von 100 willkürlich gewählten Frauen (Nicht Infarktpatienten) trat in 44 % der Fälle erhöhter Blutdruck auf. Im vorliegenden Material konnte hinsichtlich der Mortalität kein Unterschied bei Patienten mit bzw. ohne erhöhten Blutdruck festgestellt werden. Auch andere Forscher haben dieses Ergebnis erhalten (11, 31, 48, 69, 93, 115, 137). Die Mortalität der Männer wie der Frauen war im vorliegenden Material etwa gleich, obwohl erhöhter Blutdruck bei den Männern nur in 29 % der Fälle gegenüber 72 % der Frauen auftrat. Vergleicht man die beiden Hälften der Beobachtungsperiode, so erkennt man, dass eine Vermehrung der Infarktpatienten mit erhöhtem Blutdruck während der zweiten Hälfte nicht eingetreten ist.

Was den Tabak- und Alkoholgenuss der Infarktpatienten betrifft, so ging aus vorliegendem Material hervor, dass 82 % der männlichen Patienten Raucher waren, während ein Kontrollmaterial nur 63 % Raucher aufwies. Dieses Ergebnis könnte den Schluss nahelegen, dass der Tabak eine zum Auftreten von Herzinfarkt beitragende Ursache sei. Diese Ansicht äussern u.a. Hammond und Horn (65). Doch liesse sich der Sachverhalt auch so erklären, dass das Rauchen ein Zeichen dafür ist, dass Raucher nervös veranlagt und stärkerer Beanspruchung ausgesetzt sind, was einen höheren Grad von Stress hervorruft. In Cassidys Material (29) traten 82,4 % Raucher gegenüber etwa der gleichen Anzahl in einem Kontrollmaterial von Gesunden auf, was ihn zu der Ansicht veranlasste, dass die Bedeutung des Tabaks für die Entstehung von Herzinfarkt nicht besonders gross sei. Zu derselben Auffassung gelangte Blumer (17), während Yater u.a. (186) bei jungen Infarktpatienten eindeutig mehr Raucher als in einem Kontrollmaterial feststellten. Was den Alkoholgenuss betrifft, so waren 80 % der männl. Patienten des vorliegenden Materials nicht abstinent gegenüber 56,7 % in einem Kontrollmaterial. Vielleicht ist der Alkoholgenuss darauf zurückzuführen, dass es sich bei diesen Patienten um Menschen handelt, die grösserer Beanspruchung ausgesetzt wird. In Blumers Material (17) waren 42 % der Patienten abstinent und ein Kontrollmaterial zeigte ungefähr dieselben Verhältnisse, weshalb er zu der Ansicht kam, dass der Alkoholgenuss für die Entstehung des Herzinfarkts nicht von Bedeutung war. Beim Vergleich der beiden Hälften der Beobachtungszeit lässt sich feststellen, dass sich im Tabak- und Alkoholgenuss der Patienten keine Veränderungen ergeben hatten.

Was die Diät während der Beobachtungsperiode betrifft, habe ich die Cholesterolfrage nicht anschneiden wollen, weil sie mir für diesen Zusammenhang zu umfangreich war. Nachdem allerdings die Versorgungslage von Helsinki während der Beobachtungsperiode von grösster Knappheit zu normalen Verhältnissen überging, habe ich den Butter-, Fleisch-

Tabelle 49 zeigt die Zahlen des Butterverkaufes nach den Angaben der grössten Buttergrosshandlung am Platze durch die etwa 90 % der Butter in Helsinki abgesetzt wird.

Tabelle 49

Jahr	Butterverkauf (per kg)	
1945	2.236.000	
1946	2.219 000	
1947	1.555 000	
1948	3.275 000	
1949	6.354.000	Butterbewirt-
1950	6.936 000	schaftung auf
1951	9.287 000	gehoben 1949
1952	8 169 000	

Der Butterverkauf in Helsinki.

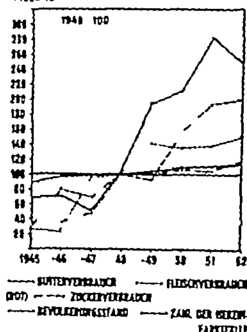
Tabelle 50 beleuchtet den Zuckerverkauf in Helsinki bei den beiden grössten Kolonialwarenketten, "Elanto" und "HOK" Diese Zahlen stellen ungefähr 35 % des Zuckerabsatzes in Helsinki dar Angaben für das Jahr 1945 waren leider nicht erhältlich.

Tabelle 50

Jahr	Zuckerverkauf (per kg)	
1946	2.192.000	
1947	2.883 000	
1948	6 193 000	Zuckerbewirt
1949	6.209 000	schaftung auf
1950	6.570.000	gehoben 1948
1951	6 427 000	
1952	7.298.000	

35 % des Zuckerabsatzes in Helsinki.

Wie die Tabellen erweisen, trat im Verlauf der Untersuchung d.i. zwischen den Jahren 1945—1952 in der Versorgungslage von Helsinki eine durchgreifende Veränderung ein. Gleichzeitig konstatieren wir eine Erhöhung der Herzinfarktfrequenz mit nicht weniger als 548 % Obwohl es in diesem Zusammenhang nicht gestattet sein kann, zwischen Lebensmittelverbrauch und Herzinfarktfrequenz direkte Rückschlüsse zu ziehen, wurde Figur 10 ausgearbeitet. Diese Figur gibt in fünf Kurven 1) die Einwohnerzahl 2) die Herzinfarktfrequenz und 3) 4) 5) den Verbrauch von Zucker Fleisch und Butter für die Jahre 1945—1952 in Helsinki.



Übersicht über die Anzahl der Herzinfarktfälle in den Helsinkier städt. Kliniken, über den Fleisch Butter und Zuckerkonsum und den Bevölkerungsstand der Stadt Helsinki.

menden Forschung vorbehalten nachzuweisen, ob eine derartige Auffassung mit der Wirklichkeit überein stimmt. Umfassende, von Amerika aus betriebene Untersuchungen sind zur Zeit in verschiedenen Weltgegenden im Gange, um diese Frage zu beleuchten.

statistisch gesehen natürlich eine Schwäche ist. Um -soweit irgend mög lich -eine grössere Genauigkeit zu er zielen wurde Figur 11 ausgearbeitet. Diese Figur beleuchtet den Zucker verbrauch per Einwohner in ganz Finnland während der Jahre 1945—1952.

Wie die Figur zeigt war der Zucker verbrauch in Finnland mit der für Helsinki angelegten Kurve gleich.

Es wurde auch versucht, der Entwicklung des Lebensstandards in Helsinki während der Beobachtungsperiode nachzugehen doch erwies es sich als ganz ausserordent lich schwierig einen Artikel aus findig zu machen, dessen Konsum auch während der Bewirtschaftungszeit für den Lebensstandard charak teristisch genug gewesen wäre. Der Autohandel z.B konnte nicht herangezogen werden, weil er sehr streng bewirtschaftet war Dasselbe gilt für Leder und Stoffwaren (Schuhe und Konfektion) Ein möglicherweise geeigneter Gegen stand wäre der Verkauf von Rund funkempfängern, aber auch hier konnten keine befriedigenden Resul tate erzielt werden, weil über den Absatz von Radiogeräten keine Sta tistik zu Gebote steht. Zwar existiert eine Statistik über die Hörerlizenzen, da man jedoch mit einer Lizenz mehrere Apparate betreiben konnte, war auch dieser Weg nicht gangbar Es wurde schliesslich der Versuch gemacht, das Steueraufkommen der Stadt Helsinki per Einwohner zu ver folgen, aber da die Besteuerungsprinzipien während der Beobachtungsperiode Veränderungen unterworfen wurden, musste auch diese Art einer Statistik unbefriedigend bleiben.

Deshalb mag die in Tabelle 52 gegebene Statistik über das finnische Volkseinkommen während der Jahre 1945—1952 wohl noch am besten in der Lage sein einen Überblick über die Entwicklung des Lebensstandards während dieser Zeit zu geben. Die hier veröffentlichten Werte stammen aus dem amtl. "Statistischen Jahr buch für Finnland Jahrgang 195"

Tabelle 52

Jahr	Total Volumen	per Einwohner
1945	76	81
1946	88	90
1947	94	95
1948	100	100
1949	105	104
1950	111	108
1951	122	118
1952	121	116

Indexzahlen für das Real Volkseinkommen in Finnland während des Zeitraums 1945—1952 1948 = 100.

Wie die Tabelle zeigt, stieg das Realvolkseinkommen während der Beobachtungsperiode bedeutend an. So lag der Wert für 1952 55 % über dem des Jahres 1945 Unter Einbeziehung der Bevölkerungszunahme bedeutete das eine Zunahme von 43 %

Auch dieser Umstand stützt die Auffassung, dass der Lebensstandard während der Jahre 1945—1952 erheblich anstieg

tungsperiode eine prozentuale Zunahme der Patienten unter 50 J. erfolgte. Eine klare Zunahme der Patienten über 70 J. liess sich für das Ende der Beobachtungszeit beweisen. Hinsichtlich der Mortalität ergab sich weder männliche noch weibliche Dominanz — die Überlebensaussichten für beide Geschlechter waren etwa gleich. Das Verhältnis des Lebensalters zur Mortalität liess eine eindeutige Zunahme der Mortalität mit zunehmendem Alter erkennen.

Hinsichtlich der verschiedenen Jahreszeiten liess sich bei vorliegender Untersuchung eine deutliche Zunahme der Infarkte während der Monate Mai, Oktober November und Dezember feststellen. Die prozentuale monatliche Verteilung wies während der beiden Beobachtungsperioden keine Unterschiede auf. Was die bevorzugte Tageszeit betrifft, so zeigte sich eine erhöhte Frequenz während der Morgenstunden von 6—9 Uhr und während der Nachmittagsstunden von 12—16 Uhr.

Das Material wurde in Sozialgruppen eingeteilt und die prozentuale Verteilung innerhalb dieser Gruppen wurde mit der prozentualen Verteilung der Sozialgruppen der Bevölkerung in Helsinki verglichen. Hierbei zeigte sich im Verhältnis zu den statistischen Zahlen ein häufigeres Auftreten von Infarktfällen bei Sozialgruppe I und ein geringeres bei Sozialgruppe IV. Das Material zeigte eine männliche Dominanz im Verhältnis 65.35 bei Sozialgruppe IV dagegen lag diese Dominanz der Männer bei 52.48. Das besagt, dass in Sozialgruppe IV mehr Frauen auftraten als im Gesamtmaterial. Ein Vergleich der Entwicklung der Sozialgruppen in den beiden Perioden ergab ungefähr das gleiche Bild, abgesehen von einem leichten Übergewicht von Gruppe I. Die Gruppen I und II wurden zu einer die Gruppen III und IV zu einer zweiten Gruppe zusammengelegt, und es wurde hierauf die Tageszeit des Auftretens der Erkrankung beobachtet. Zu beobachten war eine statistisch nicht signifikante Tendenz zu erhöhter Morgenfrequenz (zwischen 6—9 Uhr) bei den Gruppen I—II und zu erhöhter Nachmittagsfrequenz (zwischen 12—16 Uhr) bei den Gruppen III—IV.

Was den Familienstand betrifft, so wies das Material entschieden mehr verheiratete Frauen auf, als es die Bevölkerungsstatistik für Helsinki vermuten liesse. Diese Tendenz verschwand mit zunehmendem Alter. Was die männlichen Patienten des Materials betrifft, so entsprach ihr Familienstand anteilsmässig den entspr. Gruppen der Bevölkerung.

Das Auftreten von Infarkten in der Verwandtschaft der Patienten des vorliegenden Materials war doppelt so häufig wie bei den Personen eines Kontrollmaterials aus Nicht Infarktpatienten. Bei den Männern der Sozialgruppen I—II traten in der Verwandtschaft verhältnismässig mehr Infarktfälle auf als bei den Gruppen III—IV. Bei den Frauen war das entspr. Verhältnis umgekehrt, ohne jedoch statistisch signifikant zu sein. Während der Periode 1945—1948 traten mehr hereditär belastete Patien

VI DISKUSSION

Während der Jahre 1945—1952 ist zweifellos eine kräftige Erhöhung der im Maria Krankenhaus gepflegten Herzinfarktfälle eingetreten. Eine ähnliche Frequenzzunahme wurde beobachtet in einem Material das durch Zusammenstellung der Herzin farktfälle aller städt. Krankenhäuser von Helsinki berechnet wurde.

Die meisten der eingangs erwähnten Autoren (s. Literaturübersicht) waren der Meinung dass ihr Material Zunahmen zeigte, doch legten sie verschiedengeartete Ansichten über die Ursachen der Zunahme vor

Eine Ursache des Anstiegs der Herzinfarkte ist natürlich die Bevöl kerungszunahme. Die Bevölkerung von Helsinki hat sich während der Beobachtungszeit um 27,0 % vergrössert, während der Anstieg der Herz infarktfälle 548 % erreicht (Tabelle 3) Der Bevölkerungszuwachs ist demnach als ein Faktor von recht untergeordneter Bedeutung anzusehen.

Eine weitere Ursache für die Zunahme der Infarktfrequenz ist das gestiegene Durchschnittsalter der Bevölkerung, das dazu führt, dass mehr Personen das "Infarktalter" erreichen (2 35 51 114, 120) Das vorliegende Material umfasst die Jahre von 1945 —1952 also den verhältnismässig kurzen Zeitraum von nur acht Jahren. Während einer so kurzen Zeit kann sich die altersmässige Zusam mensetzung der Bevölkerung kaum bedeutend verändert haben, was auch Linko (97) betonte. Dass dies auch hier zutrifft, ergibt sich aus Tabelle 11 welche zeigt, dass die altersmässige Zusammensetzung der Bevölkerung von Helsinki sich nicht wesent lich geändert hat. Der Altersverschiebung der Bevölkerung kann der Frequenzanstieg für Herzinfarkt in vorliegender Untersuchung somit nicht zugeschrieben werden.

Verschiedene Autoren waren der Meinung (15 24 35 114 120) dass die Zunahme teilweise darauf beruhte, dass die Krankheit heutzutage genauer erkannt wird und dass auch unklare und leichtere Fälle der kli nischen Behandlung zugeführt und diagnostiziert werden. Dies ist bestimmt der Fall auch im vorliegenden Material, da der Mortalitätsprozent satz beträchtlich gefallen ist, nämlich von 60 % (1945) auf 24 % (1952) Die Gesamtzunahme der Infarktfälle im vorliegenden Material beläuft sich auf 800 % gegenüber einem Satz von nur 267 % wo der Infarkt zum Tode führte. Die schweren und typischen Fälle sind somit merkbar zurückge-

VIII SUMMARY

A series of 569 patients treated for myocardial infarction at the medical departments of Maria City Hospital in 1945—1952 was studied. The object was to establish whether an increase occurred in the incidence of myocardial infarction during this period when the supply of foodstuffs varied in Helsinki from very strict rationing to fully normal conditions. Certain socio-medical aspects were taken into consideration. As far as possible two different periods i.e. 1945—1948 and 1949—1952, were compared. The number of patients treated for myocardial infarction at Maria City Hospital increased c. 9-fold (800 per cent) in the years between 1945 and 1952. The total number of patients treated for this disease in 1945 was 15 in 1952 135 The cases of myocardial infarction treated at the hospitals of the city of Helsinki during this period were summarised. It was noted that the incidence of myocardial infarction had grown by 548 per cent in spite of the concurrent 27 0 per cent increase in the population.

The mortality rate diminished during the period of observation. It was 46 per cent in 1945—1948 26 per cent in 1949—1952 The sex distribution shows a distinct masculine predominance in the total series, however changing into a female predominance in patients aged over 70 Comparison of the age and sex structure of the series with that of the total population of Helsinki showed that there was a considerably higher male incidence of myocardial infarction among subjects under 60 than might be expected from the composition of the population of the city The difference became less pronounced with age changing into female dominance among patients over 70 This female dominance among patients over 70 years of age again, is greater than might be expected from the population structure of Helsinki. The sex distribution was on the whole unchanged between the periods 1945—1948 and 1949—1952. The majority of male cases of myocardial infarction occurred at the age of 50—60 and of female cases at 60—70 There was a slight rising tendency among patients under 50 years old per cent of the total incidence of the disease during the latter part of the observation period. A distinct increase was demonstrated in the number of patients over 70 towards the end of the observation period. No clear difference between the sexes was established in the mor-

verzehrt werden. Im Oktober beginnt die Schlachtzeit mit ihren Preisabschlägen auf Schweinefleisch und Fleisch überhaupt. Hiergegen spricht allerdings die Arbeit von Roine u.a. (146) wo konstatiert wird, dass der Fettanteil der Ernährung während der einzelnen Monate des Jahres sehr unterschiedlich ist. Bean (8,9) der eine Infarkthäufung im Winter kon statiert hat, ist der Ansicht, dass diese auf vergrössertem Infektionsrisiko und erhöhtem Gesamtstoffwechsel im Winter beruht. Ekvall (48) verzeichnet die meisten Infarkte im Quartal Sept. Nov und konstatiert, dass nicht die Kälte an dieser Häufung Anteil hat da in Nordschweden Dezember Januar und Februar die kältesten Monate sind. Das Ergebnis vorliegender Untersuchung fällt hierin also zum grossen Teil mit den Resultaten Ekvalls zusammen.

Wie die Literaturübersicht zeigte herrschte bei den herangezogenen Forschern keine Einmütigkeit hin sichtlich der Bedeutung der Tageszeit der Erkrankung Im Material von Bean (7) waren die meisten Patienten entweder am Morgen oder am Abend erkrankt im Material von Ejrup und Nylin (47) in der Nacht, und nach Master u.a. (109 111) war die Tageszeit für das Auftreten von Herzin farkt bedeutungslos Das vorliegende Material zeigte eine Häufung in den Morgenstunden (6—9) und in den Nachmittagsstunden (12—16)

Eine Reihe von Forschern ist der Meinung, dass Beruf und Sozialklasse für das Auftreten von Herzinfarkten keine Rolle spielen (30 76 91 111 141 152) während nach Ansicht anderer Forscher "sitzende" Arbeit das Auftreten von Herzinfarkten begünstigt (13 24 48 53 54 121 122, 174 186) Ryle und Russel (150) ha ben mitgeteilt dass die Mortalität bei Herzinfarkt mit sinkendem sozialen Standard zurückgeht und zwar sowohl bei Männern wie bei Frauen Auch Bronte-Stewart (25) wies da rauf hin, dass die Herzinfarktfrequenz proportional mit dem Sinken des sozial-ökonomischen Standards zurück gehe Vorliegendes Material erbrachte bei Sozialgruppe I verhältnismässig mehr Fälle als es die Zusammenset zung der Bevölkerung von Helsinki vermuten liesse Das Umgekehrte zeigte sich für Sozialgruppe IV Interessanterweise traten in Sozialgruppe IV des vorliegenden Materials verhältnismässig mehr Frauen als in den anderen Sozialgruppen auf was also den Schluss nahelegt, dass das Infarktrisiko armer Frauen grösser ist als das wohlhabender Ist als Ursache hierfür der stärkere "Stress" anzusehen dem Frauen dieser Gruppe ausgesetzt sind? Da die Zunahme der Herzinfarktfrequenz im vorliegenden Material so überaus gross war wurde untersucht, inwieweit sich eine der Sozialgruppen besonders vergrössert hat. Es ergab sich hierbei ein kleines Übergewicht der Sozialgruppe I doch war dieses nicht gross genug um statistisch signifikant zu werden.

Im Material mehrerer Forscher überragt die Anzahl der verheirateten Frauen die der unverheirateten bedeutend (7 24 109 150) Auch in vorliegender Arbeit sind die weibl.

series. The sex distribution and mortality among patients with recurrent myocardial infarction was nearly the same as among patients suffering their first attack of the disease. The frequency of recurrent myocardial infarction increased somewhat (statistically not significant) during 1949—1952.

High blood pressure was established in 38 per cent of the cases. The incidence in women was 72 per cent. The incidence of hypertension was high among female patients also in two control series of non-myocardial infarction patients. The mortality rate among patients with and without hypertension was nearly the same. A point of interest was the fact that the mortality rate was almost identical for men and women although 72 per cent of the women of the series had hypertension against only 29 per cent of the men.

A greater percentage of men used alcohol and tobacco in the myocardial infarction series than in one of the control series. The male mortality rate was practically the same for smokers and non-smokers. By contrast, the male mortality rate for those who used alcohol was somewhat lower than among the teetotallers but their mean age was also lower

During the observation period the consumption of butter and meat increased markedly in the latter but not the consumption of sugar An increase in the incidence of myocardial infarction accompanied the increased consumption of butter and meat. The standard of living rose considerably during the same period.

schiedener Forscher gefunden. Die Angaben über früheres Vorkommen von Stenokardie bei Infarktpatienten variieren im Material der bei der Literaturübersicht zitierten Forscher zwischen 33,3 % bis 73 % (11 38 44 48 53 76 113 119 141 151 186) Da Stenokardie ein subjektives Symptom ist, dürfte das Schwanken der Resultate der einzelnen Forscher verständlich sein. Im vorliegenden Material hatten 66 % der Patienten früher stenokardische Beschwerden gehabt.

Inwieweit eine frühere Stenokardie auf die Prognose Einfluss ausübt, ist eine Frage in deren Beantwortung die Forscher keine Einmütigkeit aufweisen. Ein Teil der Autoren (30 44 95) war der Ansicht dass Patienten mit vorangegangener Stenokardie kleinere Überlebenschancen haben während andere (11 151) der Meinung sind dass sich die Prognose nicht verschlechtert. Im vorliegenden Material war die Mortalität für Patienten mit vorangegangener Stenokardie ungefähr die gleiche wie bei anderen. Die Anzahl der Patienten mit vorangegangener Stenokardie war in den beiden Hälften der Beobachtungsperiode ungefähr gleich.

Bei einem Ansteigen der Herzinfarktfrequenz überhaupt kann man auch eine Zunahme der Rückfallinfarkte vermuten. So äusserte Biörck (13) den Gedanken, dass die vergrösserte Herzinfarktfrequenz vielleicht z.T auf dem Eintreten von Rückfällen beruhe. Im vorliegenden Material nahmen die Rückfälle während der zweiten Hälfte der Beobachtungsperiode etwas zu, aber nicht statistisch signifikant. Insgesamt verzeichnet das Material 1" % Rückfallinfarkte was etwas unter der von Biorck (13) angegebenen Zahl liegt jedoch z.B Eckerströms Material (44) übertrifft Hinsichtlich der Mortalität bei Rückfallinfarkten war Linden (95) der Ansicht dass sich die Prognose bei Rückfallinfarkten nicht verändere während sich in Biörcks Material (13) eine grössere Mortalität bei Rückfallinfarkten zeigte. In einer späteren Arbeit haben indessen Blomquist Sievers und Biörck (16) konstatiert dass die unmittelbare Mortalität bei Ruckfallinfarkten nicht grösser war als die bei Erstinfarkten. Im vorliegenden Material war die Mortalität der Ruckfallinfarktpatienten etwas grösser als die der Erstinfarktpatienten doch ist das Ergebnis leider statistisch nicht signifikant.

Eine Reihe von Forschern (7 11 15 29 30 31 48 62, 112, 113 133 141 152, 186) hat darauf hingewiesen dass Herzinfarktpatienten auffallend häufig erhöhten Blutdruck haben. Besonders markant sei das bei Frauen (48 93 112 119 133, 151) Im vorliegenden Material zeigte sich erhöhter Blutdruck bei 38 % der Patienten gegenüber 36 7 % bei einem Kontrollmaterial von Nicht Infarktpatienten. Ein ungefähr gleiches Resultat haben auch andere Forscher erhalten (33 38 44 74 93 151 176) ohne allerdings ein Kontrollmaterial vorzulegen. Auch im vorliegenden Material wiesen die Frauen in besonders grossem Umfang erhöhten Blutdruck auf, nämlich 72 % Eine Ursache hierfür mag darin bestehen, dass das Durch-

50. Falk, J J Amer Med. A s. 1947 134 491
51. Fitzhugh G und Hamilton, B J Amer Med. As 1933 100 47
52. Gertler M Garn, S. und White P J Amer Med. Ass 1951 147 621
53. Gertler M Driskell, M., Bland, E F Garn, S M Lerman, J., Levine, S., Sprague, H. und White, P J Amer Med. A s 1951 146 1291
54. Glendy R., Levine S und White, P J Amer Med. Ass 1937 109 1775
55. Gofman, J Jones, H., Lyon, T Lindgren, F Strisover B Colman, D und Herring, V Circulation 1952 5 119
56. Gofman, J Coronary Heart Disease. Springfield, Illinois 1959
57 Gordin, R. Nord med. 1953 49 593
58. Gordin, R. XXVII Nord. Kongr f innere Med. Oslo 1960
59 Gordon, I. Med. Officer London 1955 28 256
60. Gramm, H. Dtsch. Gesundheitswesen 1957 12 409
61. Graybiel, A., Starr R. und White, P Amer Heart J 1938 15 89
62. Gross, H. und Engelberg, H. Amer J Med. Sc. 1940 199 621
63 Halonen, P und Autio, L. Ann. med. int. Fenniae 1952 41 23
64 Halonen, P Finlands läkartidn. 1957 2 52
65 Hammond, E. und Horn, D J Amer Med. Ass. 1958 11 1294
66. Hansen, F Nord. med. 1957 58 169
67 H berden, W ref Ryl J and Russel, W Brit. Heart J 1949 11 370
68. Hegglin, R. Ztschr Präventivmedizin 1959 4 439
69 Helander S Cardiologia 1950 15 347
70. Hellmuth, G Illinois Med. Bull 1947 92 86
71. Henschen, H. Svenska läkartidn. 1950 47 2269
72 Hilleboe H. J Cronic dis 1937 6 210
73 Hipsley E. H. Nutr Rev 1958 16 129
74. Hochrein, M und Schneyer K. Ztschr kreisl. forsch. 1936 28 2.7
75 Ikkala, E. und Kalpalnen, W Ann. med int. Fenniae 1957 46 155
76. Jacobs, T Ann Int Med. 1951 34 114
77 Jensen, D Diskussionsprotokoll. Det Norsk Medicinske Selskab Nord. Med. 1959 6. 1050
78. Jervell, A Acta med. Scand. 1933 suppl 68
79 Jervell, O und Ettinger L Nord med 1950 43 160
80 Johnson, W Archer R., Burchell, H und Edwards, J Arch Int Med 1959 103 2.3
81 Järvinen, K. Brit. Med. J 1955 5 318
82. Järvinen, K. Finland läkartidn. 1960 25 1423
83. Kappert, A. Schweiz. Med. Wschr 1959 89 34
84 Karvonen, M. Koutalous 1958 1 3
85 Keys, A. Voeding 1952 13 539
86. Keys, A., Bronte, S Brook, J Moodie, A., Haney Keys, M. and Antonis, A. Circulation 1955 12 730
87 Keys, A. Brit. Med. J 1956 July 14 98
88 Keys A. J Amer Med. Ass. 1957 164 Aug. 24 617
89 Kristenson, A. Svenska läkartidn. 1949 46 1550
90. Knervnski ref Klin. Wschr 1925 1 39
91 Lee, K. und Thomas W Arch. Int. Med., Chicago 1956 97 421
92. Lew E. J Chronic Dis 1957 6 197
93. Levine, S und Brown, C. Medicin 1929 8 245
94 Levine, S und Hindle J N England J Med. 1945 233 657
95. Linden, L. Acta med. Scand. 1952 143 464
96. Lindhart, M. Danish Med. Bull. 1954 1 179
97 Linko E. Duodecim 1954 7—8
98. Lundqvist, C. und Björnwall, J Svenska läkartidn. 1936 33 1209
99 Lups, S und Francke, C. Acta med. Scand. 1947 126 449
100. Luten, D Amer Heart J 1931 7 36
101. MacKenzie, J Brit. Heart J 1949 11 4
102. Malmros, H. Nordisk med. 1949 42 1785
103. Malmros, H. Acta med. Scand. 1950 suppl. 246
104 Martin, W Brit. Med. J 1956 1 1323
105. Master A. M., Jaffe, H. und Dack, S. Proc. Soc. Exper Biol Med., N Y 1934 —35 32 779
106. Master A. M. J Amer Med. Ass 1935 105 337
107 Master A. M., Jaffe, H. L. und Dack, S J Clin. Invest. 1936 15 353
108. Master A. M Dack, S. und Jaffe, H. L. Amer Heart J 1937 13 330
109 Master A. M., Dack, S und Jaffe, H. L. J Amer Med. Ass. 1937 109 546
110. Master A. M., Jaffe, M und Dack, S N Y Stat J Med. 1939 39 1937
111 Master, A. M Dack, S und Jaffe, H. Amer Heart J 1939 18 434
112. Master A. M., Dack, S und Jaffe, H. L. Arch. Int. Med., Chicago 1939 64 767
113. Master, A. M., Dack S und Jaffe, H. N Y State J Med 1942 42 413
114 Master A. M Amer Heart J 1947 33 135

und Zuckerverbrauch während der angegebenen Zeit beobachtet.

Einen Zusammenhang von Hungerzeiten und niedrigerer Herzinfarktfrequenz der Bevölkerung haben verschiedene Forscher nachgewiesen (12, 71 83 102, 139 164) Das vorliegende Material zeigt, dass der Butter und Fleischkonsum im Verlauf der Verbesserung der Ernährungslage in Proportion zum Frequenzanstieg des Herzinfarktes gestiegen ist. Die Konsumzunahme bei Zucker liess dagegen mit der Normalisierung der Lebensmittellage im Jahr 1948 nach. Die Zuckerverbrauchs-Kurve verläuft von da an nicht mehr parallel zu den Kurven für den Fleisch- und Butterkonsum und den Herzinfarkt.

In vorliegender Abhandlung wurden sozial-medizinische Faktoren untersucht, die möglicherweise auf die Entstehung von Herzinfarkt Einfluss haben konnten. Es ergab sich, dass die nachstehend aufgeführten Faktoren bei den Patienten des vorliegenden Materials auch statistisch signifikant in Korrelation zum Auftreten von Herzinfarkten stehen.

1 Geschlecht
2. Alter
3 Monat der Erkrankung
4 Tageszeit der Erkrankung
5 Sozialklasse
6. Familienstand (bei weibl. Patienten)
7 Heredität
8 Butter und Fleischkonsum.

Ich habe in vorliegender Arbeit eine Frequenzzunahme der im Maria Krankenhaus zu Helsinki behandelten Herzinfarktpatienten während der Jahre 1945—1952 nachgewiesen in einer Zeit zu der die Versorgungslage in Helsinki von strenger Lebensmittelknappheit zu normalen Verhältnissen überging. Die Ursachen für diese Frequenzzunahme waren die folgenden.

1 Die Bevölkerungszunahme
2. Die Aufnahme leichterer Fälle
3 Erkranken einer beträchtlich grösseren Anzahl älterer Personen gegen Ende der Beobachtungszeit.
4 Gegen Ende der Beobachtungszeit war eine Zunahme von Patienten der Sozialgruppe I zu verzeichnen, doch war dieses Ergebnis statistisch nicht signifikant.
5 Gegen Ende der Beobachtungszeit nahm die Anzahl der Rückfallinfarkte etwas zu, doch war dies Ergebnis statistisch nicht signifikant.

Diese fünf Faktoren reichen zur Erklärung der Frequenzzunahme nicht aus sie muss auf weiteren Ursachen beruhen, die im Verein mit den veränderten sozial-ökonomisch-diätären Lebensbedingungen der Bevölkerung von Helsinki während des beobachteten Zeitraums aufgetreten sind.

Man fühlt sich versucht, auf Basis vorliegender Untersuchung dem gestiegenen Lebensstandard und vielleicht der vergrösserten Kalorienzufuhr eine gewisse Bedeutung für den Frequenzanstieg des Herzinfarktes in Helsinki während der Beobachtungszeit zuzuschreiben. Es bleibt der kom-

VII ZUSAMMENFASSUNG

Zweck vorliegender Untersuchung war es festzustellen, inwieweit die Herzinfarktfrequenz in Helsinki eine Zunahme zeigt in einer Periode während der die Versorgungslage von strenger Bewirtschaftung zu völlig normalen Verhältnissen überging. Im Zusammenhang damit wurden bestimmte sozial-medizinische Gesichtspunkte, über welche unten mehr gesagt wird, mit in Betracht gezogen. Soweit überhaupt möglich wurden Vergleiche zwischen den beiden Unterperioden der Beobachtungszeit, nämlich 1945—1948 u. 1949—1952 vorgenommen. Die Anzahl der wegen Herzinfarkt ins Maria-Krankenhaus aufgenommenen Patienten zeigte von 1945—1952 einen Anstieg von 800 %: gegenüber 15 Patienten 1945 wurden 1952 135 gepflegt. Über die zur fraglichen Zeit in sämtlichen städt. Krankenhäusern von Helsinki aufgenommenen Infarktfälle wurde ein Verzeichnis angelegt, aus dem sich ergab, dass die Herzinfarktfälle eine Zunahme von 548 % gegenüber einer Bevölkerungszunahme von 27.7 % zeigen.

Der Verfasser hat ein Material von 569 Infarktpatienten untersucht, die während der Jahre 1945—1952 auf den Inneren Abteilungen des Maria-Krankenhauses gepflegt wurden.

Die Mortalität zeigte für die Beobachtungszeit eine Abnahme. Während der Periode 1945—1948 lag sie bei 46 %, während der Periode 1949—1952 dagegen bei 26 %. Was die Anfälligkeit der Geschlechter betrifft, so zeigt das Material als Ganzes betrachtet männliche Dominanz, während in den Jahrgängen über 70 Jahre die Frauen dominieren. Beim Vergleich von Alter und Geschlecht der Patienten des Materials mit der Zusammensetzung der Bevölkerung von Helsinki war zu konstatieren, dass bei Personen unter 60 Jahren bedeutend mehr Infarkte bei Männern auftraten, als die Zahl für die entspr. Bevölkerungsgruppe erwarten liess. Der Unterschied wurde mit zunehmendem Alter weniger markant und ging bei einem Alter von 70 J. und mehr in weibliche Dominanz über. Diese Dominanz ihrerseits war grösser als es die entspr. Gruppe der Bevölkerung erwarten liess. Ein Vergleich der beiden Beobachtungsperioden 1945—1948 und 1949—1952 ergab keine wesentlichere Veränderung. Die meisten Fälle lagen bei den Männern zwischen 50—60 J., bei den Frauen zwischen 60—70 J. Es liess sich eine gewisse Tendenz beobachten, nach der im Material während der zweiten Beobach-

ten auf als in Periode II (1949—1952) das Verhältnis war 35 % zu 25 %.

66 % der Patienten des Materials hatten schon früher an stenokardischen Beschwerden gelitten. Die Mortalität dieser Patienten war etwa gleich gross wie die der früher stenokardiefreien Patienten. Während bei der Perioden war die Anzahl der Patienten, die an stenokardischen Beschwerden gelitten hatten, ungefähr gleich gross.

17 % des Materials umfasste Rückfallinfarkte. Sowohl die Geschlechter Gliederung wie die Mortalität war bei den Rückfallinfarktpatienten ungefähr die gleiche wie bei den Erstinfarktpatienten. Die Periode 1949—1952 zeigte eine leichte statistisch nicht signifikante Zunahme der Rückfallinfarktfälle.

Bei 160 mmHg syst. Druck als Grenzwert ergab sich ein erhöhter Blutdruck bei 38 % aller Fälle (72 % der weibl. Fälle). In zwei Kontrollgruppen wurde auch bei weiblichen Patienten in zahlreichen Fällen Hypertonie festgestellt. Die Mortalität der Patienten war bei Hypertonie ungefähr gleich hoch wie ohne.

Nicht uninteressant ist die Beobachtung, dass die Mortalität der Frauen und der Männer etwa gleich war obwohl in 72 % der weibl. Fälle des Materials, dagegen nur in 29 % der männl. Fälle Hypertonie auftrat.

Prozentual gesehen waren mehr männliche Patienten Raucher und nicht-abstinent als die Männer eines Kontrollmaterials. Die Mortalität der männlichen Raucher und Nichtraucher war etwa gleich, dagegen war die Mortalität der nicht abstinenten Männer etwas niedriger als die der abstinenten, doch war ihr Durchschnittsalter etwas niedriger.

Was die Ernährungslage während der Beobachtungsperiode betrifft, so hatte der Fleisch- und Butterkonsum während der zweiten Periode (1949—1952) entschieden zugenommen, während der Zuckerkonsum sich nicht wesentlich verändert hatte. Eine Frequenzzunahme der Herzinfarkte zeigte graphisch denselben Verlauf wie der Anstieg des Butter- und Fleischverbrauchs. Der Lebensstandard zeigte während dieser Zeit einen kräftigen Anstieg.

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tality rate men and women had roughly equal chances of survival. As regards the relationship between mortality and age a distinct increase in the death rate was established with age.

The incidence of myocardial infarction by seasons showed a distinct increase in the present series during May and October—December. The percentual distribution between the different months of the year was the same during 1945—1948 and 1949—1952. The time of the day of the onset of the disease on the other hand, showed that the incidence was higher during the morning hours (0600—0900) and the afternoon (1700—1800).

The series was divided into social groups and the percentual distribution of these groups was compared with the corresponding percentual distribution of the population of Helsinki. The myocardial infarction percentage was higher in social group I and smaller in social group IV than could be expected from the statistics for the total population of the city. While the male predominance of the series as a whole was 65.35 the male female ratio in social group IV was 52.48. Women were thus proportionately more numerous in social group IV than in the total series. Comparison between the periods 1945—1948 and 1949—1952 showed that all social groups had increased in roughly the same ratio social group I showing a slightly greater rate. Social groups I and II were combined and groups III and IV likewise to form two groups which were then compared for the time of the day of the onset of the disease. A tendency (statistically not significant) to increased incidence in the morning was observed in social group I—II and in the afternoon in social group III—IV.

The analysis by marital status revealed more married women with myocardial infarction than the composition of the population of Helsinki presupposed. This tendency disappeared with age. For male patients the percentual distribution by marital status concurred with that of the total population.

The patients in the series reviewed showed double the incidence in their family history of that of a control series of non-infarction patients. Social group I—II displayed a relatively higher male familial incidence of myocardial infarction than social group III—IV. The reverse was true of the women, but the difference was not statistically significant. There were more patients (35 per cent) with hereditary symptoms in 1945—1948 than during the later period (25 per cent).

Of the total series 66 per cent had suffered earlier from stenocardiac complaints. The mortality rate was roughly the same for the patients without stenocardiac complaints and for those afflicted by them. The number of myocardial infarction patients with a history of stenocardiac trouble was approximately the same during both observation periods.

Recurrent myocardial infarction accounted for 17 per cent of the

IX LITERATURVERZEICHNIS

1. Ahn, B v Nord. med. 1949 41 451
2. Albert, H. J Amer Med. Ass 1927 89 1312
3. Alvord, T M. Arch. Int Med. 1949 84 1002
4. Andersson, B. Svenska läkartidn. 1930 47 2997
5. Appelbaum, E. und Nicolson, G Amer Heart J 1935 10 663
6. Baud, H. W Kaubeum. Fortbild.—Lehrg. 1959 34 889
7. Bean, W Amer Heart J 1937 14 684
8. Bean, W Ann. Int. Med. 1938 12 71
9. Bean, W und Mills, C Amer Heart J 1938 16 701
10. Berg, H. Dtsch. med. Wschr 1954 79 801
11. Billings, F T Kalstone, B. M Spencer J L., Ball, C.O.T und Meneely C R. Amer J Med. 1949 7 356
12. Biörck, G und Blomqvist, N Soc med. tskr 1949 10—11 213
13. Biörck, G., Overbeck, O und Grönvall, C. Cardiologia 1954 25 4
14. Bjerkelund, C. J Acta med. Scand. 1957 suppl. 330
15. Bland, E. und White, P J Amer Med. Ass 1941 117 1171
16. Blomqvist, G., Sievers, J und Biörck, G. Acta med. Scand. 1960 167 301
17. Blumer G J Amer Med Ass 1934 102 1177
18. Boas, E J Amer Med. Ass. 1939 112 1887
19. Boas, E. Amer Heart J 1942 23 1
20. Bonsdorff B. v Acta med. Scand 1939 100 403
21. Bonsdorff B. v Svenska läkartidn 1945 38 2365
22. Bor I. Schweiz. med. Wschr 1939 34 899
23. Borgström, G. Svenska läkartidn. 1951 48 532
24. Brahme, L. und Ahlberg. J Svenska läkartidn 1947 46 2177
25. Bronte-Stewart, B., Keys, A. und Brock, J Lancet, London 1955 2 1103
26. Bryant, M., Arbor, A. und Wood, J Jr Amer Heart J 1947 34 20
27. Buff L J Amer Med. Ass. 1955 157 569
28. Burstein, J Acta med. Scand. 1953 suppl 285
29. Cassidy M Lancet, London 1946 2 587
30. Chambers, W N England J Med 1946 235 347
31. Chambers W Amer J Med Sc. 1947 213 40
32. Chapman, J M., Goerke, L. S Dixon W Loveland, D. B. und Phillips, E. Amer J Publ Health 1957 suppl. April 33
33. Conner L. und Holt, E. Amer Heart J 1930 5 705
34. Dawber T R., Moore, F E. und Mann, G. V Amer J Publ. Health 1957 suppl. April 4
35. Davidson, W Med J Australia 1933 40 584
36. Davis, F Scarborough, Wm., Mason, E. E., Singewald, M. L. und Baker B M. Amer Heart J 1956 51 165
37. Dock, W Med. Clin. North America 1953 866
38. Doscher N und Poindexter C. Amer J Med. 1950 8 623
39. Dotzauer G. und Naeve, W Dtsch. Zschr Gerichtl Med. 1956 43 30
40. Doyle, J Heslin, S., Hilleboe H., Formel, P und Korns, R. Amer J Publ Health 1957 suppl. April 25
41. Doyle, J Heslin, S., Hilleboe, H. und Formel, P N England J Med 1959 261 1096
42. Duguid, J Lancet, London 1954 I 891
43. Duguid, J und Robertson, W Lancet, London 1955 I 325
44. Eckerström, S Acta med. Scand 1951 suppl. 250
45. Ehrström, M Ch. Nord. Med. 1950 44 1823
46. Ejrup B Nord Med. 1943 18 1058
47. Ejrup, B. und Nylin, G. Nord Med. 1943 20 2163
48. Ekvall, S Cardiac Infarcts Umeå 1955
49. Enos, W Holmes, R. und Beyer J J Amer Med. Ass 1953 152 1090



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HELSINKI

115. Ma t A. M., Dublin, L. und Mark H J Amer Med. As 1950 143 1464
116. Master A. M. und Jaff H. J Ame Med. Ass 1952 148 794
117 Mattila, A.: Duodecim 1938 6 401
118 Miller D C Stare F J und Whit P D J Amer Med. A s. 1956 .3 329
119 Mintz, S und Katz, L. Arch Int Med Chicago 1943 80 205
120. Morris, J N Lancet, London 1951 1 69
121. Morris, J N Heady J A., Raffl P Roberts, C. und Parks. J Lancet, London, 1953 2 10 3
1__ Morris J und Crawford, M Mod. Med. 1959 27 193
123 Morrison L. J Amer M d A 1960 173 884
124 Munck, W Acta path. microbiol Scand 1946 23 107
125. Neth, R. und Schwarting, G Dtsch. med Wsch 1935 15 570
126. Newman, M Lancet, London 1951 1 1045
127 Nikkilä, E. Scand J Cl In t 1953 uppl. 8
128 Noro, L. Työ ja Terveys 1956 4 12
129 Nylin, G Nord med 1943 18 1045
130 Oliver M F und Boyd, G S Minnesota Med. 1955 38 794
131 Ott, W Schweiz. Zschr für Volkwirtschaft und Statistik 1949 85 343
132. P ge, L, Stare, F Corcoran, A., Pollack H und Wilkinson, C Circulation 1957 16 163
133 Palme J. Lancet, London 1937 1 741
134 Parker R., Dry T., Willius, F und Gage, R J Amer Med A 1946 131 95
135. Pat rson, J J Amer Med. A s. 1939 112 893
136 Peel, A. Brit Heart J 1955 17 319
137 Pell, S und D'Alonzo C. J Amer Med Ass. 1958 166 332
138 Phipps C J Ame Med A 1936 106 761
139 Pierach A. Münch Med Wsch 1958 100 1527
140 Raffi, E und Oppenheimer B Proc Exper Biol Med N Y 1928 26 9
141 Rathe H J Amer Med A 1942 120 99
142. Rauterberg, W Dtsch Gesundheitswesen 1957 12 325
143. Riesman, D und Harris, S Amer J Med Sc 1934 187 1
144 Roen, P Towsend, E und Perry J Circulation 1951 4 471
145 Roine, P Pekkarinen, M Karvonen, M und Kihlberg, J Lancet, London 1958 26 173
146. Rome, P und L kila, H Kotilalou 1959 2 35
147 Rosenbaum, F und Levine S Arc Int M d Chicago 1941 68 913
148. Russel, H Zohman, B Doerner A Russel A. und Wh t C J Ame M d. Ass. 1951 14 1731
149 Ru sek H Zohman, B. und Dorn t A J Amer Med. Ass 1955 157 563
150. Ra J und Ru sell, W Brit Heart J 1949 11 370
151 Räsänen, M : Duodecim 1951: suppl. 21
152. Scherf D und Boyd, L. Klinik und Therap de H erzkrankh und Gefässerkrankungen, Wien 19 1
153 Schettler G. Verh. Dt ch Inn Med. 1934 60 683
154 Schmidt L Lancet, London 1935 2 1341
155 Schnur S A n. Int. Med. 1956 44 4 6
156 Schwei W Ztsch Prä entivmedi n 1939 4 4.4
157 Segal H. Amer J Med. Sc. 1938 196 851
158. Shaffer C und Chapman, D Cor ela tis Cardiology Philad lphia und London, 195_
159 Sjövall, H. nd Wahman, G Act path microbiol. Scand 1934 suppl 20 1
160 Smith, H. J Amer Med. A 193 108 1327
161 Sprague H. Med. Cl n North Ame 1953 1283
16_ Sterner P Arch, of Path 1946 4 3
163. Ströder, U Becker, F nd Haa C Kl Wschr 1951 29 312
164 Ström, A und Jensen, R N rd. hyg T k 1950 123
165. Ström, U und Rygh, A. Nord med 1952 47 396
166 Tannenbaum, O Vesell, H und Schack, J Circulation 1955 12 783
167 Tar jew E. Inne e Krankheiten, Moskau 1952, ref Pierach, A Münch. Med Wsch 1958 100 1527
168 Thomas, C und Cohen H Ann. Int. Med. 1955 42 90
169 Thompson, W Med Cl North America 1952 991
170 V rpela, E. Nord Med 1960 63 127
171 V rtiainen, I und Kanerva, K. Ann med. int Fenniae 1947 36 748
172 Wecker B Dtsch Arch. Klin. Med 1940 185 393
173 Wespi, H Ztschr Prä ent vmedizin 1959 4 413
174 Westlund, K und Hougen, A. Acta med Scand 1956 154 315
175 Whit P J Amer Med. A s. 1926 87 1525
176 White, P und Bland E. Amer Heart J 1931 7 1
177 White, I und Sha ber T J Amer Med A s. 1934 102 655

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Helsinki, February 1961

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ACTA MEDICA
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SUPPLEMENTUM 363

EXFOLIATIVE CYTOLOGY IN GASTRIC MALIGNANCY

With special reference to the diagnostic significance of nuclear size and mitotic frequency

BY
KARI SEPPÄLÄ

ACCOMPANIES VOL. 169

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1945 Tanner 1944 Schindler 1950 Gutman 1951 Jemerin and Colp 1952 Lehtinen et al 1960)

By the time the above diagnostic methods are used, the gastric neoplasm has often already metastasized and as a result the chances of permanent recovery even after successful surgery are slight. Of th series reported by Berkson and his coworkers (1952) of gastric cancer patients subjected to either laparotomy or palliative surgery approximately 5 per cent were alive 2 years after the operation, 5 years after operation the figures were 0 7 per cent for the laparotomy group and 1 per cent for those who had undergone palliative surgery According to the same report, 14 per cent of all gastric cancer patients operated on curatively or subjected to explorative laparotomy were alive 5 years after surgery

Results depend, among other things, on the operating techniques employed. In a total gastrectomy series the mortality on operation is higher than in a series with subtotal gastrectomy Yet in the total gastrectomy series reported on by Fly and his co-workers (1958) for example the five year survival rate was 12 per cent while in many series consisting largely of subtotal gastrectomies this survival rate was lower (Welch and Wilkins Jr 1958, Gusa 1951 Ransom 1955 McNeer et al. 1958, Tuomikoski 1957 Blomquist 1956) If a review of the survival rates of different series includes only those cases in which a gastrectomy was performed the survival prognosis is somewhat improved Berkson and his co-workers eported for their series a five year survival rate of 31 (per cent for the gastrectomized cases of gastric carcinoma, in Ransom's series the percentage was ?8 and in that published by McNeer and his co-workers 25.8 In Finland, Blomquist reported a 5-year survival rate of 16 per cent for patients subjected to gastrectomy

To improve therapeutic results in gastric carcinoma the disease should be diagnosed at such an early stage that it has not yet had time to spread widely into the surrounding tissue or to metastasize. For this reason, gastric cancer ought to be demonstrable in the almost asymptomatic stage, and special attention should therefore be devoted to patients with a gastric ulcer or to those groups of patients known to run a higher risk of contracting gastric cancer These groups comprise elderly patients suffering from pernicious anaemia, gastric polypi, and possibly also from atrophic gastritis (e.g Kaplan and Rigler 1945 Berkson et al 1952 Hitchcock et al. 1957 Siurala et al 1959 and 1960)

Efforts have been made to diagnose gastric carcinoma in the asymptomatic stage by mass x-ray examination (St. John et al. 1944) and by performing frequent check-ups of the patients listed above as being predisposed to gastric cancer Several gastric cancers have in fact been diagnosed in the asymptomatic stage by these methods (State et al 1950) but the methods themselves are of little practical importance in the improvement of the early diagnosis of gastric cancer

In the drive to achieve better therapeutic results, all new types of examination should however be tested in order to find other diagnostic methods for use side by side with x rays.

EXFOLIATIVE CYTOLOGY IN GASTRIC MALIGNANCY

REVIEW OF LITERATURE

Historical Review

Exfoliative cytology is usually the study through stained smears, of individual cells or clusters of cells which have become detached either spontaneously or artificially from their environment. Over a century ago in 1843 Walshe found small fragments of tumour tissue in the saliva of patients with carcinoma of the respiratory tract. This was probably one of the first examples of the cytological demonstration of tumour cells.

The earliest recorded references in the literature to gastrointestinal cytology date back at least to 1858. In that year William Brinton in his book "Lectures on the diseases of the stomach" discussed the haemorrhages connected with cancer of the stomach but mentioned another symptom which had until then been almost completely ignored, viz. the finding of characteristic cancer cells in vomit. Brinton stated that, in addition to the usual difficulties encountered in microscopic diagnosis of a cancer the disturbing effect of gastric juice and gastric content had also to be taken into account. H recommended the removal of excessive bl od or bil by the cautious add tion of water nd th ubsequent filtration of solids for microsc pi [illegible] Where microscopic examination [illegible] be performed immediately he [illegible] syrup the best preservative Brinton declared that it was not difficult for the trained eye" to distinguish even half digested cancer tissue from the epithelial cells of the oesophagus or the stomach, but mere isolated cells or nuclei scarcely justify a decision.

In the 1870's mucosal fragments were found to have been detached by the stomach tube during examination but detachment of epithelial fragments was considered dangerous and was not generally known to be useful for diagnosis. Rosenbach, as late as 1882, again suggested that attention be given to tumour fragments found in the gastric content aspirated or vomited H himself had found such fragments in three cases of gastric carcinoma

By the 1890's, several investigators had found tumour fragments in the gastric juice, and some text books cla med that their demonstration was of significance in the diagnosis of gastric cancer Rosenheim (1896) for example considered that demonstration of tumour fragments in vomit or gastric-lavage sediment was the only infallible pathognomonic symptom of gastric cancer Ewald (1093) described tumour fragments he had found in the gastric sediment of gastric carcinoma patients, but warned that such f gments were easily mixed with frag

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of Anatomy at Cornell University had concentrated his studies on the normal and abnormal variations of human and animal vaginal smears. He found that, in cases of cancer in the uterine body and in the uterine cervix, cancer cells were exfoliated into the vagina and could be shown by taking a specimen of the vaginal excretion which was stained according to a method he had himself developed Papanicolaou and Traut were able to show accurately on the basis of cytologic criteria malignancy in 123 out of 127 vaginal smears of patients with carcinoma of the uterine cervix. In the same way they found cells classified as cancer cells in 46 out of 53 specimens of the vaginal excretion of patients with cancer of the uterine body

The study of 220 vaginal smears, reported on in the same year by Meigs and his co-workers (1943) corroborated *the promising results of the investigation* by Papanicolaou and Traut Of the 62 specimens from patients with a malignant growth in the reproductive organs only two showed no cells classified as malignant on cytologic examination The cytologic method was reaccepted before the end of the Second World War for the examination of excretions secretions or lavage specimens from various organs. It was not long before papers on the cytologic diagnosis of gastric carcinoma were published.

Methods used in gastric cytology

Lavage with saline solution. In the early studies cytologic preparations were made either from ordinary post fasting gastric sediment or from sediment after gastric lavage with saline solution It was understood that gastric retention interfered with the examination and it was known that rapid fixation of the smears was essential to prevent deterioration of cells exfoliated from the stomach. Yet in spite of this — and although the Papanicolaou method was employed to stain the preparations — cytologic examination indicated malignancy only in about half the cases of gastric neoplasm Furthermore, examination of patients with non malignant gastric diseases quite often produced a cytologic finding which falsely suggested malignancy Gradually however the results began to improve as new methods and more reliable interpretation of the cytologic samples became possible.

In 1947 Papanicolaou and Cooper published their results on a series of 137 patients, 27 of whom had proved gastric *cancer* Of these cases of *carcinoma*, 10 were cytologically diagnosed as malignant, and the specimens of another 7 patients were suspected to be malignant. Ten samples remained negative, while of the specimens of the remaining 110 patients, in whom no indication of a malignant growth in the stomach had been found none was falsely diagnosed malignant by cytological methods. In the following year (1948) Graham Ulfelder and Green reported on a series of 50 gastric patients. Gastric cancer had been diagnosed in 24 patients, the diagnosis based on cytology in 15 cases. In one case the cytologic diagnosis was falsely positive. Two cases which on cytologic examination were considered malignant proved on operation to be extremely early malignant lesions in the stomach.

PREFACE

Cytological examination of the stomach was introduced in the University Central Hospital of Helsinki, Out Patients Department of Medicine, in 1956 on the initiative of a team led by Docent Wilhelm Kaipainen, M.D. It was soon clear however that successful cytological examinations demanded close cooperation between the Department and the Cytological Laboratory. It was therefore decided that, as a member of the team, I should learn the cytological method of diagnosis. Both Docent Kaipainen and Professor Harald Teir M.D., subsequently recommended the present subject for my doctoral dissertation.

The actual work described was carried out under the direction of Professor Teir Head of the Department of Pathology Section II University of Helsinki. Since I was a clinician, Professor Teir had first to train me as a cytologist. He did so without sparing himself, and his continued guidance throughout the study has been of greater value than the writer of a dissertation might possibly hope for. I am greatly indebted to him.

I should also like to extend my warmest thanks to Professor Ilmari Vartiainen, M.D. Head of the Second Department of Medicine, University of Helsinki, for having provided me with such excellent laboratory facilities and for giving ready advice throughout the period of study. I am very grateful too to Docent Kaipainen for his continued interest in my work and for his good advice and encouragement. I am indebted to Docent Max Siurala, M.D. for the gastric biopsy specimens which he provided for me, for the instruction in gastroenterology which he gave and particularly for the valuable suggestions he made when the actual writing of the paper was begun. My thanks are also due to the other clinical members of the Department, who in the good spirit characteristic of the Department, have assisted me in my work.

The medical and other staff of other hospitals and pathological laboratories have always been ready to help, when necessary in the different phases of my work. I am particularly indebted to Professor Väinö Seiro M.D. Head of the Second Surgical Department, and to Professor Olavi Perasalo, M.D., Head of the Third Surgical Department, University of Helsinki, for putting at my disposal the case histories of patients operated on in their departments. I am equally grateful to Professor Erkki Saxén, M.D. the then Chief of the Pathological Laboratory of the Department of

of Anatomy at Cornell University had concentrated his studies on the normal and abnormal variations of human and animal vaginal smears. He found that, in cases of cancer in the uterine body and in the uterine cervix, cancer cells were exfoliated into the vagina, and could be shown by taking a specimen of the vaginal excretion which was stained according to a method he had himself developed. Papanicolaou and Traut were able to show accurately on the basis of cytologic criteria, malignancy in 123 out of 1[illegible] vaginal smears of patients with carcinoma of the uterine cervix. In the same way they found cells classified as cancer cells in 46 out of 53 specimens of the vaginal excretion of patients with cancer of the uterine body.

The study of [illegible]20 vaginal smears, reported on in the same year by Meigs and his co-workers (1943) corroborated the promising results of the investigation by Papanicolaou and Traut. Of the 6[illegible] specimens from patients with a malignant growth in the reproductive organs only two showed no cells classified as malignant on cytologic examination. The cytologic method was reaccepted before the end of the Second World War for the examination of excretions, secretions or lavage specimens from various organs. It was not long before papers on the cytologic diagnosis of gastric carcinoma were published.

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Lavage with saline solution. In the early studies cytologic preparations were made either from ordinary post fasting gastric sediment or from sediment after gastric lavage with saline solution. It was understood that gastric retention interfered with the examination and it was known that rapid fixation of the smears was essential to prevent deterioration of cells exfoliated from the stomach. Yet in spite of this — and although the Papanicolaou method was employed to stain the preparations — cytologic examination indicated malignancy only in about half the cases of gastric neoplasm. Furthermore examination of patients with non-malignant gastric diseases quite often produced a cytologic finding which falsely suggested malignancy. Gradually however the results began to improve as new methods and more reliable interpretation of the cytologic samples became possible.

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CONTENTS

ERRATA

Page 13 – line 16 from above, left column: Salzmann not Salzmann
18 – 19 from below right column: 1951 not 1930
21 – 9 from above, right column. Cooper not Seybolt
79 – 7 from above, right column: Tornenius not Tornelius
79 – 9 from above, right column: Tornenius not Tornelius
Add to page 79 – line 12 from above, left column: Schindler R.: Gastritis.

tion for screening purposes was suggested to 71 patients who had shown no symptoms indicative of gastric cancer 65 attended for the examination but only a total of 41 could in fact be examined, the rest either refused to submit to the process or failed despite their efforts to swallow the balloon. On the basis of this experience Chapman and his colleagues came to the conclusion that the method was good from the cytologic point of view since suitable patients yielded excellent slides, but on the other hand the balloon study was not readily accepted by the patients and was too time-consuming to be useful as a routine examination method for gastric cancer

Enzyme lavage methods. The gastric mucosa is covered by a mucous layer which protects the epithelium but, by its mere existence, prevents cells exfoliated from the gastric mucosa from freely entering the stomach. On the other hand a large number of cells detached from the upper respiratory tract and the alimentary canal and swallowed into the stomach are trapped in the mucus. In conventional physiological saline lavage, the viscosity of the mucus in the lavage solution has been found to inhibit the sedimentation of cells on centrifuging and as a result the smears might show only a few cells. Enzyme lavage is useful because enzyme solution is effective on both counts. on the one hand, it dissolves the mucous layer protecting the epithelium, with the result that more gastric cells are exfoliated into the lavage fluid, and on the other by dissolving the mucus, it promotes the sedimentation of cells on centrifuging In addition, the use of enzyme solution might increase the exfoliation of cells in cases of neoplasm. As a rule, the amount of normal epithelial cells found in gastric lavage specimens is fairly small, considering the large surface area of the gastric epithelium. This is due to the fact that the reaction of healthy tissue to lavage is different from that of a carcinoma. One of the properties of the gastric surface epithelium, as of any healthy epithelial tissue is that the cells tend to adhere to each other while in malignant tissue adhesion between cells has been found to be much weaker (Coman 1944 McCutcheon Coman and Moore 1948) Proteolytic enzymes may perhaps, weaken the adhesiveness of tumour tissue cells still further by loosening the cement substance which holds the cells together thus producing a still greater exfoliation of malignant cells. This explains why with the use of enzymatous methods, better results may be expected than by other methods.

Rosenthal and Traut (1950) while trying to discover a suitable substance with a mucolytic effect, found that the enzyme papain, with a proteolytic effect, was a good solvent of mucus and reported that the cellular returns on the lavage material (after the fasting specimen was discarded) have been uniformly abundant, without noteworthy cellular degeneration. The papain method is simple and quick to perform, but its drawback is that well preserved cells are not regularly obtained since the papain may besides dissolving the mucus, destroy exfoliated gastric cells. This is understandable since the papain employed is a crude mixture of enzymes, of varying activity The use of the method is further hampered by the fact that the papain solution must always be prepared

INTRODUCTION

The stomach is one of the organs in which cancer may most frequently be found, and the patients who contract gastric cancer are usually middle-aged or elderly people. Statistics have been published in several countries on mortality rates for gastric cancer, but since it is often impossible to operate, or even to examine old people in such a way that a potential gastric neoplasm might be finally proved, statistical errors are possible. For this reason Doll (1956) excluded the highest age groups from a study in which he compared the death rates in gastric cancer among men between the ages of 35—4. On the basis of the mortality statistics in a number of different countries, it was revealed that the annual incidence of cancer deaths per 100 000 men of this age was 220 in Japan, 209 in Iceland, 131 in Norway and 116 in the Netherlands, but only 65 in Venezuela and 76 non-white and 48 white men in the USA. Although diagnostic standards are not the same in all countries nor mortality statistics based on identical examinations of patients, the incidence of gastric cancer obviously varies considerably from one country to another. For Finland, Doll quoted a figure of 216/100 000. According to data published by Saxén and Korpela (1958) however only 132 cases of gastric cancer per 100 000 men in these age groups were diagnosed in Finland in 1954 and the death-rate quoted by Doll is thus too high. The incidence of gastric cancer is definitely higher among men than among women, the incidence figure for women is only 50—67 per cent of that for men.

In the last few decades x-ray findings have been used to provide the diagnostics for gastric cancer. The number of gastric neoplasms correctly diagnosed radiologically in different materials varies from 70 to over 90 per cent of the cases examined (Walters et al. 1941, Bolker 1949, Lawton et al. 1951, Gray and Ward 1952, Swynnerton and Truelove 1952, Pack 1953, Templeton 1955).

Gastroscopy is a method of examination used to supplement gastric roentgenology. A technically successful gastroscopy may provide in addition to the data facilitating differential diagnosis, information on changes of the gastric mucosa otherwise unobtainable by x-ray or clinical examination. Gastroscopy therefore has its place in the diagnosis of gastric neoplasms although a gastric neoplasm can be diagnosed with the same accuracy as by gastric x-ray only if the patients have been preselected (Pollard and Cooper

logical smears obtained by the "Zelltupfsonde" method, Henning and Witte (1957) described the cytologic finding in cases of various types of gastritis and other gastric complaints. In their experience, gastritis might be cytologically diagnosed if the cells had increased. The cellular picture of surface gastritis is dominated by the presence of high prismatic mucosal surface cells, occurring in large clumps and numbers. An acute exacerbation of gastritis can be identified by the occurrence of leucocytes, which lie intracellularly. Leucocytes found extra-epithelially play a minor role in diagnosis. They occur in certain numbers in a normal stomach and increase in numbers following a variety of stimuli. Atrophic gastritis leads to characteristic alterations of the surface epithelium corresponding to the degree of intensity of the chronic inflammation. There are marked morphological changes in the mucosal cells exfoliated in large numbers. High cylindrical cells are scanty compared with the plump cylindrical and round forms. Cellular atypism is seen increasingly showing itself as marked anisokaryosis, binucleation, increased size of nucleoli, variable staining of cytoplasm with intensive basophilia and loss of cell boundaries. Goblet cells and epithelial cells with striated border may be seen as a sign of alteration of gastric epithelium into intestinal epithelium.

The most pronounced changes in the superficial epithelium are to be seen in pernicious anaemia. Histologically the stomach shows mucosal atrophy and loss of gastric glands, inflammatory cell infiltration and metaplasia (e.g. Schindler 1947, Siurala 1954). In addition to the changes seen in atrophic gastritis and listed above, cytologic study also reveals cells unusually large in size (Graham and Rheault 1954, Massey and Rubin 1954). The cell nuclei are also large, while frequently the nuclear membrane assumes a typical creased or folded appearance, and small aggregates of chromatin stand out against the relatively empty background of the nucleus. The cytoplasm occasionally appears more vacuolated and granular than normal. Perinuclear halos or half moon shaped vacuoles may be seen. Massey and Rubin (1954) called these cells "P.A. cells" and though they found them originally only in pernicious anaemia they later discovered them in atrophic gastritis without haematological evidence of pernicious anaemia (Henning and Witte 1957).

The incidence of glandular cells proper in the gastric sediment has been taken as an indication of continuous marked gastric secretion, and glandular cells may therefore be particularly expected in patients suffering from duodenal ulcers. The finding usually consists of chief cells containing basophilic granules, and parietal cells with larger cytoplasm. Mucous neck cells are difficult to recognize cytologically.

Cytologic study has naturally been primarily concerned with the diagnosis of neoplasms. Certain criteria for malignancy have already been formulated for practical purposes: according to the Staff of the Vincent Memorial Hospital (1950), Hjelt (1953), Panico (1953), Papanicolaou (1954), Henning and Witte (1957) and others, the malignant nucleus is characterized by the varying size and

Positive experience has been gained on the diagnostic value of exfoliative gastric cytology in cases where the diagnosis has already been made by some other means of examination. No report on a large series examined cytologically has yet been published to illustrate the specific use of the method for the diagnosis of gastric carcinoma in its early stage. Only when cytologic gastric examination is more widely used will it be possible to establish clearly first, the importance which an examination method based on the exfoliation of gastric cells may have in the diagnosis of gastric neoplasms and, second, whether by this method gastric cancer patients can be operated on sufficiently frequently at such an early stage that the current unsatisfactory prognosis of the disease may be improved

Table 1 The results obtained by different cytologic methods in some series previously reported on.

Year	Authors	Method: lavage	Method: mechanical	Method: enzyme	Total Series	Malignant Cases Cytologic finding: Cases	Malignant	Suspicious	Negative	Non-malignant Cases Cytologic finding: Cases	Correct	False-suspicious	False-positive
							%	%	%			%	%
1947	Papanicolaou and Cooper	–			137	27	37	26	37	110	91.5	8.5	–
1948	Graham et al.	–			50	24	62.5		37.5	26	96		4
	Fremont–Smith et al.	–			193	63	54			128	97.7		2.3
1949	Bryant et al.	–			392	61	45.5	14.5	40	306	94		6
	Andersen et al.		–		[illegible]	42	93		7	92	98		2
	Richardson et al.	+			235	27	48		52	51	96		4
1950	Botsford and Tucker	+			124	23	74		26	101	96		4
	Swarts et al.	+			166	67	44		56	99	90		10
1951	Seybolt et al.	+			875	168	33	18	49	707	87.5	10	2.5
	Friedrich	+			96	21	38	4	58	75	93	4	3
	Daiber et al.		+		32	18	67	22	11	15	73	27	–
1952	Traut et al.			–	400	42	70	7.5	22.5	358	99		1
	Hemming and Witte[8]		+		145	33	61.5	22.5	16				
1953	Cooper and Papanicolaou		+		238	51	74.5	13.5	12	187	94.5	5	0.5
	Rubin et al.		+	+	111	42	83		17	69	96		4
1954	Ayabe et al.	–			236	117	66	8.5	25.5	119	95	3	2
1955	Klayman et al.			+	313	75	80		20	238	98	0.4	1.6
	Rubin, Benditt[8]			+	64	20	95		5	44			
1955	Zamcheck et al.	–	–		122	8	87.5		12.5	114	99		1
	Jeschal		+		78	30	67	16.5	16.5	80	90	9	1
	Browne et al.[11]		+		[illegible]	17	23.5	35	41.5	39	100	–	–
1956	Conte and Conte-Marti		+	+	110	30	61	33	6	80	90	9	1
	v.d. Reis et al.			+	70	8	50	25	25	62	90.5	9.5	–
	Sicard et al.		+	+	51	14	65		35	37	89	11	–
1957	Seybolt and Papanicolaou		–		602	117	66	19	15	485	94.4	5.4	0.2
1958	Ross et al.[13]		–	+	232	41	71	5	24	134	99	0.5	0.5
	Umiker et al.			+	116	38	65	24	11	78	92	5	3
	Zelazowski		+		161	66	70	18	12	95	94	6	–
	Bremner et al.			+	60	15	67		33	45	100	–	–
	Rachur and Lambling[15]		+	+	163	52	6	4.5	19.5	111	89	5	6
	Raskin et al.	+			501	98	95		5	403	99.3		[illegible]
	Fischman et al.		+		48	18	72	6	22	30	90	6.5	3.5
1960	Bech–Nielsen and Amdrup			+	60	14	79	14	7	46	93.5		6.5
	Nieburgs et al.		+		93	38	52.5		47.5	55			4
	Raskin et Plencka[1]	–			1208	154	94		6	1054	99.6		0.4
	Schade[14]	–			2443	258	90.5		9.5	264	95		3

ments of tissue aspirated from a gastritic stomach Ewald felt that he was unable to distinguish between the single cancer cells which might be found in the specimens and the other macronuclear cells of the squamous type gastric cells or individual nuclei.

In Finland the method was in use at the latest by 1893 when Runeberg reported that two cases of gastric carcinoma had been diagnosed on the basis of tumour fragments obtained by aspiration though such examination was not, however generally or even periodically practised. This is supported by the fact that Saltzmann 1913 describing 54 gastric cancer patients operated on since the turn of the century did not mention any one of them as having been diagnosed in this way

In the United States, Hemmeter (1899) reported on an abrasive method by which the gastric wall was scraped with a soft gastric tube. In this way he assumed tumour tissue could be detached from the tumour even when the tumour did not ulcerate He considered his method harmless and had found no complications in his series of 48 cases of gastric carcinoma.

Even at this date opinions varied concerning the value of cytologic examination of the stomach Boas (1897) and Ewald (1893) considered cytologic diagnosis difficult and found that it was sometimes impossible to distinguish between tumour cells and normal mucosal cells Similarly Reineboth (1897) doubted the diagnostic value of cytologic examination even though he noted certain differences in the structure of normal cells and tumour cells. Ehmer (1908 and Sahli (1913) on the other hand, felt that the diagnosis of gastric cancer could be based on a cytologic finding

Marini (1909) tried to prove that, in fresh, unstained smears tumour cells could be distinguished from the normal cells of gastric mucosa. His series consisted of 37 cases of gastric carcinoma in the gastric lavage fluids of 3 of the patients he found fragments of tumour tissue but individual tumour cells were present on 32 occasions. Marini concentrated on the size of the cell, of the nucleus and of the nucleolus. On comparison he found that normal cells were definitely smaller and he felt that it was now possible to distinguish tumour cells from ordinary cells present in gastric specimens. Loeper and Binet (1911) used stained preparations to study the gastric sediments in different gastric complaints.

Interest in gastrointestinal cytology seems gradually to have declined there after Attention was focused instead on the advances in roentgenology of the stomach, and no important papers on cytology of the stomach were published for many years Admittedly Zemansky (1928) analysed the quantities of tumour cells found in different fluids but he felt that the study of the gastric content was of little value in the diagnosis of gastric carcinoma. More promising results were reported by Frahman and Gorin (1942) who found tumour cells in the gastric sediment of 20 out of 45 patients with gastric carcinoma.

Cytologic study gained greater impetus after Papanicolaou and Traut (1943) published their report on cases of uterine cancer diagnosed by means of vaginal smears. G N Papanicolaou Professor

this it can be seen that only the Papanicolaou group later replaced the conventional lavage method (Papanicolaou and Cooper 1947) by the mechanical abrasive balloon method (Seybolt and Papanicolaou 1957). A comparison of the results obtained by these two methods reveals that findings indicative of malignancy have increased from 51 to approximately 85 per cent. The improved result would suggest that the mechanical method may yield somewhat better results than mere lavage. On the other hand Ayabe with his co-workers (1954), Schade (1955) and Raskin et al. (1960), among others, using the conventional lavage methods obtained results fully comparable with or even better than, those Seybolt and Papanicolaou achieved by the abrasive balloon method. Good results have been systematically achieved by using either the enzyme lavage method alone (e.g., Traut et al. 1952, Rubin and Benditt 1955, Klayman et al. 1955) or a combined enzyme lavage and mechanical method (e.g. Rubin et al. 1955, Conte & Conte-Marti 1956, Richir and Lambling 1958). As a rule, according to the various reports, over two-thirds of all cases of neoplasm have been successfully diagnosed cytologically, and no studies based on these methods have yielded a completely negative result.

Fremont-Smith, Graham and Meigs (1948) studied a series of 193 patients 65 of whom had proved gastric carcinoma. Cytologic examination gave a positive result in 35 cases (54 per cent) and a falsely pos tive result in 3 cases (2 per cent) This resea ch team considered it quite possible that gastri carcinoma might be diagnosed earlier by cytology than by other methods

Some authors, however arrived at a more negative conclusion egarding the value of cytologic examination in the *diagnosis of gastri carcinoma* This was fully understandabl since e.g Kreuz feldt (1944) managed to f nd cells inter preted as malignant in only 2 out of 17 examinations made on gastric cancer patients. Polla d t al. (1949 nd Mar cussen and Myttung (1950 aga n felt that at that time this diagnostic method should not provide the exclusiv basis for either the positive diagnosis or the posi tive exclusion of gastric neoplasm. Fried rich (1951) diagnosed 38 per cent of his 21 gastric cancer cases by means of cytology and 90 per cent roentgenologi cally As a result, he concluded that the cytological examination of gastric sediment could not have any practical importance compared with roentgenolo-gical examination.

Reports have subsequently been published however of series in which examination of the ordinary gastric sed-iment has yielded much better results. The Japanese authors Ayabe, Ota and Izaki (1954) out of a series of 117 gastric cancer cases, cytologically diagnosed 66 per cent as malignant and another 8.5 per cent as suspicious, while in 2 cases (5 per cent) of a series of 119 patients with no proved gastric cancer the cyto-logic finding had been falsely interpreted as malignant. This material also demon-strated that the stomach had to be completely clean and empty before the cytologic examination The authors e ported that there were frequent unclean pecimens with many foreign elements or considerably degenerated cells which prevented the detection of cancer cells Diagnosis was 92 per cent accurate in cancer cases with clean smear specimens, wh le with unclean specimens it was only *17 per cent accurate.*

Schade (195(of the United Kingdom, obtained good results — particularly in the diagnosis of early gastric carcinoma — using ord nary gastric sediment and saline lavage. After a prel minary examination of the specimens of some 500 patients, 70 of them were operated on on the basis of cytologic suspicion of malig nancy 64 of the cytologically diagnosed cases of gastric carcinoma were verified histologically 25 had already been diag nosed clinically *and* roentgenologically while in 29 cases the clinical nd x ray findings were doubtful and the diagnosis of gastric carcinoma was corroborated by cytologic examination. In 10 cases the diagnosis was based on the cytologic finding alone. Three of these showed incipient carcinoma in connection with atrophic-hyperplastic gastritis. The re maining 6 of the patients operated upon were found, histologically to have chronic atrophic hyperplastic gastritis.

In 1959 Schade reported that his material on gastric cytology already consisted of 3,500 cytologic examinations of the stomach, including 16 in which a malignant lesion confined to the mucosa

THE SERIES

The hospital system in Finland has been planned and part realised on the basis of a number of local hospitals supplemented where required, by better equipped central hospitals. The country has accordingly been divided into 21 central hospital districts. The University Central Hospital of Helsinki the biggest hospital in the country is both a university teaching hospital and the central hospital of Uusimaa Administrative District. The hospital, though principally for patients from the city of Helsinki and from elsewhere in Uusimaa District, does accept patients for examination from all over the country The Out Patients Department of Medicine, where the patients of the present series were examined usually admits patients for examination only if they are recommended by physicians or other hospitals.

The Cytologic Laboratory In 1956 a cytologic laboratory was established in the Out Patients Department of Medicine for the collection of gastric cell specimens* A specially employed laboratory nurse took the cell specimens, dyed them, and later assisted at their screening The writer was both attending physician and cytologist of the laboratory and received skilled guidance in the interpretation of the cytologic specimens from Prof. H. Teir M.D (Department of Pathology Section II University of Helsinki) In 1957 the laboratory began to supply its own independent statements on the specimens studied but Professor Teir has been continuously consulted.

Indications for examination. In the circumstances the indications for examination were relatively broad, but no attempt was made at a systematic examination of all gastric patients attending the Department during the period. The object was to perform a cytologic examination of patients who on the basis of clinical or x ray examination, were suspected of gastric cancer Cytologic examination was also automatically performed on patients who during the period of the study submitted to gastroscopy in the Out Patients Department or Second Department of Medicine. The principal indications for gastroscopy were: (1) a suspected malignant x ray finding, (2) an uncertain x-ray finding, (3) a negative x-ray finding in gastric complaints, and (4) gastric ulcer All proved cases of gastric neoplasm, however were not sent for cytologic examination since it would have been unreasonable to make

* President J K. Paasikivi's Foundation for Cancer Research awarded grant for the purpose.

to be used in conjunction with fluoroscopy which is a limitation. Ayabe with co-workers (1954) tried to detach cells from the gastric lesion by means of a metal "olive" attached to a gastric tube, but the method had to be abandoned because of the risks of haemorrhage and perforation. Kuttelwascher (1954) suggested the use of a small concentrated jet of water connected with a gastric tube for the exfoliation of cells.

Ruiz Martinez (1958) made a triple lumen tube using a current of air from a compressed air cylinder to exfoliate gastric cells, part of the air current ran straight through one lumen into the stomach and part through another lumen into lavage solution (Ringer or saline) which it forced along a second section into the stomach. The mixture of air and lavage-fluid now entering the stomach was expected to detach tumour cells better than would be possible if conventional lavage techniques were employed. Aspiration occurred through the third lumen of the tube. Raskin and Pleticka (1960) employed a method by which lavage solution could be forced quickly into the stomach by an air compressor and quickly re-aspirated. In addition, they used a magnet to locate the end of the lavage tube both in the body and more particularly in the antrum during the examination.

Of all mechanical methods designed for the collection of specimens for gastric cytology however the abrasive balloon method developed by Panico, Cooper and Papanicolaou (1950) seems with various modifications, to have been most extensively used. This method was based on an abrasive instrument consisting of a double lumen tube which ends in a net covered balloon. After preliminary lavage the balloon is inflated in the fundus and then carried distally by peristalsis. It is then pulled back gently until a mild gag reflex is produced and the procedure is repeated. The balloon is deflated withdrawn and agitated in Ringer's solution to remove the cells. Well preserved epithelial cells are obtained individually and in sheets. By this method, Seybolt and Papanicolaou (1957) were able to diagnose cytologically 6 out of 117 (66.6 per cent) cases of gastric carcinoma and in another 20 cases (17.6 per cent) the cytologic finding was suspicious (Class III). They considered this a useful, supplementary method of examination to be used in conjunction with gastric roentgenology.

There have been many subsequent modifications of the "abrasive balloon". Rubin and his co-workers (1953) fitted a mercury weight to the end of the gastric tube to help antral abrasion. With the patient in the lateral decubitus position the weight passed into the duodenum (or was at least meant to do so) after which the balloon was inflated and pulled back towards the cardia, exercising an abrasive effect on the antrum. On deflation the weight again passed into the duodenum, and the antral abrasion could be repeated. Further modifications have been described e.g. by Jeschal (1955) and Zeligowski (1958).

The use of the balloon is not entirely without discomfort because it is difficult to swallow. Chapman, Klopp and Platt (1955) tried to investigate the potential use of the abrasive balloon as a screening test for gastric cancer. Balloon examina-

- operative data for patients operated on,
- information about cause of death in fatalities.

In addition an enquiry was circulated to patients whose later vicissitudes would not otherwise have been known, copies of the circulars are attached (Appendix 2)
- follow-up procedure also included a check with the Cancer Registry* that patients who had failed to answer the letter of inquiry had not been entered as gastric cancer cases.

Table 2. Basis for the diagnosis in the 151 cases of malignant neoplasm and the 585 negative cases with regard to gastric neoplasm of the present series.

Malignant group 151 cases	Cases
Diagnosis for malignancy based on:	
Operative finding and biopsy	92
Autopsy	4
Operation	4
Clinical finding and biopsy	15
Previous laparotomy and biopsy	2
Clinical findings, follow-up and posthumous information	34

Non-malignant group 585 cases	Cases
Diagnosis negative with regard to malignancy based on.	
Operative finding	119
Autopsy finding	11
Clinical follow-up examination	119
Data obtained by correspondence	269
Follow-up and posthumous information	10
No personal follow-up data	57

The grounds on which the material is divided into the *malignant* and the *non malignant groups* are given in Table 2 where the data obtained on follow-up examinations is also taken into account.

Verification of malignancy As already mentioned, the *malignant group* numbered 151 patients, in 96 of whom the clinical diagnosis of neoplasm was verified by laparotomy In two cases considered inoperable on laparotomy no neoplasm was found in the specimens taken during the operation, and in another two cases no biopsy was taken in connection with the operation In a further 19 cases, the diagnosis of malignancy was confirmed by a biopsy without laparotomy In 10 of these cases, the biopsy was taken from lymph nodes; in 5 it was taken direct from the neoplasm in connection with oesophagoscopy and in 4 cases which were not operated on, in the subsequent autopsy For two patients, the neoplasm already verified by laparotomy was detected cytologically while for the remaining 34 patients, the diagnosis of neoplasm was based solely on the clinical or x-ray examination, and endoscopy None of these patients is alive today Nine patients had a neoplasm in the distal part of the oesophagus: full details of the distribution of gastric neoplasms by localization and histologic type is given later with the results of the cytologic examination (pp 49–55)

Operative data. 76 patients of the *malignant group* were operated on in the Second and Third Departments of Surgery University of Helsinki, the remaining 20 were operated on elsewhere.

* The Finnish Cancer Registry is run by the Finnish Cancer Society with the Assistance of the Public Health Service and the Central Office of Statistics. It is based on voluntary system. All hospitals, laboratories and practising physicians are requested to inform the Registry of all cancer cases coming to their notice (Saxén, 1955)

at the moment of the examination in order to be fresh.

Traut and his co-workers (1952) in a series of 400 patients examined by the papain method, reported on 42 gastric cancer cases. Thirty of them (71 per cent) were cytologically diagnosed as malignant, but if only technically successful tests are taken into consideration the papain method according to Traut and his co-workers, could provide 85 per cent reliability in cytologic diagnosis of gastric carcinoma.

The papain method, in combination with the abrasive balloon method has subsequently been employed by e.g. Conte and Conte Marti (1956) and by Richir & Lambling (1958). This combination of the two methods seems to improve the reliability of the cytologic study, for Conte and Conte Marti obtained a cytologic finding indicative of malignancy in 94 per cent, and Richir and Lambling in 80.5 per cent, of the gastric carcinoma cases in their series.

Rubin and co-workers (1953) again, began to use crystalline alpha chymotrypsin for the dissolution of mucus employing the abrasive balloon to take specimens. Very good specimens were obtained in this way and 35 out of the 42 gastric cancer cases of the series were correctly diagnosed by cytology. Later Rubin and Benditt (1955) discarded the abrasive balloon and lavaged the stomach solely with buffered chymotrypsin solution. In this way they managed to diagnose cytologically 19 out of their 20 gastric carcinoma cases, and by the same method Klayman and his co-workers (1955) cytologically diagnosed 60 out of 70 malignant gastric tumours. The chymotrypsin lavage method has subsequently been used at several different clinics (e.g. Reis et al. 1956, Umiker et al. 1958, Brenner et al. 1958, Bach Nielsen and Amdrup 1960, Seppälä et al. 1960) and the series of patients to be reported on in the present paper has also been examined by this method.

Cellular elements in gastric smears

A study of gastric lavage sediment reveals many different cells and much cellular debris. Some of these cells come from the upper part of the alimentary canal and from the respiratory tract, and have been swallowed into the stomach with saliva or sputum. The sediment may also contain erythrocytes or inflammatory cells, possibly deriving from the stomach (Tomenius, 1946, 1947). Cells from the duodenum — and even the pancreatic and common bile ducts — may occasionally reach the stomach by reflux. For cytologic study, however, the cells deriving from the gastric epithelium are the most important. The gastric epithelium is normally composed of very regular simple columnar cells. In addition, there are gastric glands which open into the gastric pits. Lavage of the normal stomach seldom yields cells of the columnar type or cells of the gastric glands. The majority of cells encountered in smears from gastric fluid are cells carried into the stomach from the oesophagus and the oral mucosa. These are cells of the squamous type showing considerably variability in size and form.

With a diseased stomach, the cellular finding changes and the sediment contains more gastric cells. In a comparison of histological biopsy preparations and cyto-

examined showed symptoms suggestive of gastric carcinoma although explorative laparotomy a good two years earlier had revealed no gastric cancer. Because of the patient's advanced age however (83 years) and the extent of the neoplasm, no operation was performed.

Follow-up data by correspondence. Information on the state of 269 patients of the *non-malignant group* during the observation period is based on replies to the questionnaire circulated in connection with the follow-up studies. 157 of these patients reported that they were completely healthy or at least that they had no abdominal trouble worth mentioning. Slight discomfort — temporary or of a dyspeptic type — was reported by 57 patients, while 55 claimed that their abdominal trouble was unchanged though none reported an aggravation of abdominal trouble during the period of observation. Because of the symptoms reported in their replies or earlier examination findings, some of the patients were requested to attend for examination at the Out Patients' Department; accounts of these cases are naturally based on the examination and are not included in the group of data obtained by letter.

No information available. The *non-malignant group* includes 57 patients who have not answered the letter of inquiry nor have they died during the period of observation. Eleven of them had been free from gastric symptoms on discharge from the hospital, and 5 had attended the clinic for re-examination a few months after the gastric examination, but 41 patients have not been heard of since they underwent a gastric cytology examination. According to the diagnosis made after examination, none of them suffered from gastric cancer. All cases of malignant tumour diagnosed in the country are recorded in the Cancer Registry and this was accordingly consulted for information about the fate of the patients on whom no data had been obtained. None of these 57 patients, however, was recorded as having contracted gastric neoplasm.

Diseases found in the non-malignant group. The majority of patients in the *non-malignant group* suffered from a gastric disease of some kind but for a good 16 per cent, judging by the clinical diagnosis, the gastric trouble was found to be primarily attributable to diseases in other organs. Table 3 gives the control material, corrected by possible follow-up data, classified according to the diagnosis made at the time of the cytologic examination.

Table 3. The non-malignant group (585 cases) classified according to diagnosis.

Diseases of the	Number of cases	Total
Stomach		464
benign neoplasm	2	
gastric ulcer	189	
gastritis	185	
other gastric diseases	88	
Intestine		29
duodenal ulcer	21	
other intestinal diseases	8	
Liver		5
Gallbladder and bile ducts		19
Pancreas		6
Blood		24
pernicious anaemia	9	
pernicious tapeworm anaemia	8	
other blood disorders	7	
Other sites		38
		585

shape of the nuclei and by the frequent occurrence of cells with giant nuclei. The nuclei stain hyperchromatically and the chromatin net is sometimes irregular and the nuclear membrane thickened. The nucleoli are usually exceptionally large and more numerous. In addition, multinucleation, vacuolization and mitotic activity with abnormal mitotic figures may be seen. In the cytoplasm there are usually less extensive changes. The cytoplasm itself is generally scanty and the nuclear-cytoplasmic ratio is upset. The cytoplasm may be greatly vacuolized and cells of the signet ring type found, cytoplasmic inclusions such as leucocytes or cellular debris may also be present. The loss of distinct boundaries within a cluster may be considered an effect of the dedifferentiation of cells which is not uncommon in malignancy.

If major clusters of malignant cells are found in a preparation the diagnosis is not particularly difficult, but it is more difficult to conclude malignancy on the basis of individual cells. The conclusion is made even more difficult by the fact that there exists no absolute criterion by which a malignant cell can be distinguished from a benign. Cytologic assessment of malignancy must always include a comparison of individual cells suspected of being malignant with the cells in the vicinity because cytologic assessment of malignancy is based primarily on the properties of the nucleus and the cytoplasm and on whether the cells occur singly or in clusters. Cytomorphology in gastric cancer cases does not differ appreciably from that in other neoplasms of epithelial origin and similar in type, but its closer definition on the strength of cytologic preparations is nevertheless clearly impossible particularly in poorly differentiated cases. Pictures illustrating the cytologic finding in gastric carcinoma have been included in several papers (e.g., Papanicolaou 1954, Lopes Cardozo 1954, Henning and Witte 1957, Gibbs 1960).

Seybolt and Papanicolaou (1953) and Rubin and Massey (1954) on the basis of cytologic finding diagnosed as malignant lymphoma 2 out of the 4 and 4 out of the 5 malignant lymphoma cases in their respective series. They considered such a cytologic finding so typical that it sufficed to warrant a malignant lymphoma diagnosis prior to any operative measures. Rubin and Massey classify among these neoplasms those originating in the lymphoid and reticulo-endothelial cells, such as reticulum-cell sarcomas, lymphoblastic and lymphocytic lymphomas, follicular lymphomas and Hodgkin's disease. A typical cytologic finding in these cases is the observation that cells exfoliated from a lymphoma are distributed singly rather than in the crowded clumps characteristic of carcinoma. Occasional groups of cells are seen in those lymphomas that are exfoliating profusely. These grouped lymphoid cells still maintain their isolation from one another.

Summary

A number of papers on the use of the various methods of examination described above have been published since Papanicolaou and Cooper (1947) first reported on their gastric sediment studies, but results obtained for different series, even though the same method were used, are not fully comparable. Just as the size of

lateral position, were made into a special preparation. The fluid recovered was centrifuged by the Wifug centrifuge of sufficient capacity to enable all the liquid to be centrifuged at one time. The speed was 3 000 RPM. Seven smears were made of the sediment — one from the Ringer lavage and 6 from the chymotrypsin lavage. Fixation was effected immediately in the moist condition in ether — 95 % alcohol solution, for a minimum of 30 minutes. It was of paramount importance for the success of the examination to have the smears in fixation fluid not later than 10—15 minutes after collection, before the cells had been dissolved. The adhesion of the cells was promoted by treating the slides with serum before the specimen was spread or by instilling serum or Mayer's albumin into the centrifugate before centrifuging.

Oesophageal lavage. In cases of suspected carcinoma of the cardia where the lavage tube could not be introduced into the stomach, the oesophagus or cardia was lavaged with Ringer's solution. The tube was passed to the lowest possible level of the oesophagus, Ringer's solution was injected into the oesophagus as vigorously as possible by a 100 ml syringe, and the injected solution withdrawn at once. The lavage was repeated a few times with the same solution, after which the recovered fluid was set aside; the whole lavage operation was performed as described several times. Depending on the amount recovered 200—1 000 ml of Ringer's solution was employed. The centrifuging and fixation of smears was carried out in the same way as for chymotrypsin lavage.

Staining

The staining method employed was the modification developed by Papanicolaou (1954) for the staining of gastric sediment; the nuclei were stained by Harris's haematoxylin and the plasma by OG 6 and EA 65. A recognized advantage of this modification is that the smears are transparent when stained so that thick preparations containing plenty of mucus can be studied.

The actual staining instructions read as follows:

1. After fixation and without drying, transfer slides directly from alcohol-ether to 80 % alcohol and run down through 70 % and 50 % alcohol to distilled water.
2. Stain in Harris haematoxylin for 2 minutes.
3. Rinse in distilled water then 50 % alcohol.
4. Place for 1 minute in solution of 1.5 % ammonium hydroxide made up with 70 alcohol.
5. Rinse in 70 % alcohol, two changes.
6. Run up in 80 % and 95 % alcohols.
7. Stain in OG 6 for 1 ½ minutes.
8. Rinse in 95 % alcohol, two changes.
9. Stain in EA 65 for 1 ½ minutes.
10. Rinse on 95 % alcohol, three changes. Dehydrate and clear by running through absolute alcohol, mixture of absolute alcohol and xylol equal parts, and xylol.

After staining, the slides were coated with Canada balsam. When the specimens from patients having or suspected of having a neoplasm had been stained, the staining and rinsing solutions were filtered in order to avoid possible contamination of later specimens by detached malignant cells.

The study of smears and the assessment of findings

The writer personally studied all the specimens, examining the smears "blind" without any previous information about

the series may vary so does the number of cases excluded because of an unsuccessful examination or for some other reason and the results are accordingly affected. Consequently in materials which completely exclude those cases of gastric neoplasm in which the cytologic examination failed, the apparent incidence of diagnosed gastric neoplasms is higher than in similar series for which all cytologically false-negative cases are taken into account, irrespective of whether or not the examination was considered a technical failure Furthermore, the criteria by which malignancy is confirmed are not always the same; in some examinations the aim has undoubtedly been to reach a diagnosis of malignancy as reliable as possible, while in others, efforts have been made to diagnose as many cases of neoplasm as possible and the number of findings falsely interpreted as positive is then also higher Some reports make no distinction between cases interpreted as malignant or only suspected as such. To enable some kind of a comparison to be made, the results reported by the various methods have been assembled in Table 1 From

Notes to Table 1

Only 567 cases of the series were included in the results. The examination was technically unsuccessful in 6 cases of the malignant group but these cases were excluded from the negative cases entered in the table

The original series comprised neoplasms of the oesophagus and cardia, plus control cases. All the cases of cardial carcinoma and the non-malignant cases of the total series are entered in the table.

Only 78 cases were discussed in detail. The samples were unsatisfactory in 3 cases of the malignant group

There were in all 404 cases The samples of 3 cases of the malignant and 25 of the non-malignant group were unsuccessful, but these failures are excluded from the table.

There were in all 1 034 samples (including 51 oesophageal and 68 duodenal samples) of which 60 failed.

The series further included 107 cases examined by the lavage method A finding suggesting malignancy was obtained in 34 per cent of 44 carcinoma cases. The finding was false-positive in 5 per cent of the cases

The series also included 600 cases examined by the physiological saline method. Thirty out of 53 gastric carcinoma cases were diagnosed cytologically False-positive diagnoses amounted to 0.8 per cent.

The malignant group included 4 cases of oesophageal carcinoma. Two cases, in which the finding was ... have been excluded from the table

No potential false-positive results are specified.

[10] Examined by various methods, but results were not analysed.

Total series was 93 cases The table gives only the cases verified on operation.

Examined by various methods, but results were not analysed.

[13] The results do not include 6 cases of the malignant and 6 of the non-malignant groups in which no final statement was issued after the examination findings.

The examination failed in 29 cases out of the total series.

There is no report of the number of cytological re-examinations which took place when examinations had been unsuccessful for technical or other reasons.

[14] Results in operatively verified cases are reported in the table. The examination failed in 7 per cent of gastric carcinoma patients.

e.g. atrophic gastritis. Demonstration of malignancy was considered the most important object of the cytologic study and the cytologic finding was therefore specified in each case, using the following classification.

(a) *absence of cells suspected of malignancy*

(b) *inconclusive finding*

(c) *suspicious finding*

(d) *malignant finding*

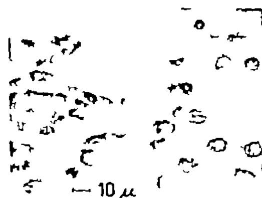


Fig. 2.



Fig. 3.

Fig. 2. *Absence of cells suspected of malignancy*. P.A. cells with enlarged nucleus in the middle and lower part of the photomicrographs, and some striated border cells with smaller but more hyperchromatic nuclei on the left. To the far right a squamous epithelial cell. Bioptical specimens revealed gastric ulcer with atrophic gastritis. Case 167/57

Fig. 3. *Inconclusive cytologic finding*. On surgical exploration nothing unusual was found in the stomach. Case 121/57

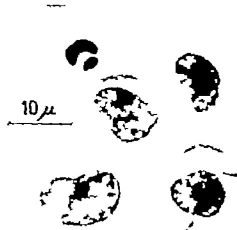


Fig. 4

Suspicious cytologic finding. Bioptically gastric adenocarcinoma. Case 61/59

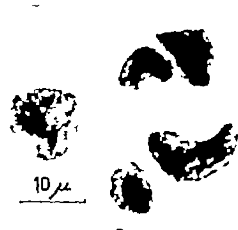


Fig. 5.

Malignant cytologic finding. Bioptically solid gastric cancer. Case 14/59.

OBJECT OF THE PRESENT INVESTIGATION

The principal reason for the poverty of therapeutic results in gastric neoplasm is the scarcity and vagueness of the early symptoms of gastric carcinoma, as a result of which the diagnosis usually comes too late for successful operative treatment. Attention should therefore be given to all the examination methods by which current diagnostic reliability might be improved. Exfoliative gastric cytology is one such method. Assessments of its importance seem to vary. The variety of the results obtained may be ascribed to: (1) the absence of uniform criteria, (2) differences in methods of examination, (3) the examination of smears by different individuals and (4) the limited size of many of the series. Furthermore, earlier papers on gastric cytology did not pay much attention to assessing the importance of certain individual signs of malignancy. For these reasons the writer felt the need to study the clinical importance of exfoliative gastric cytology using the chymotrypsin method and studying a sufficiently large series. At the same time, biopsy specimens have been used to assess the significance of nuclear size and mitotic division as criteria of malignancy in gastric cytology.

The problems posed for the present investigation were:

1. How often can a gastric neoplasm be shown cytologically?

2. How often does cytologic examination yield a false-positive finding?

3. Are the results of cytologic examination correlated or supplementary to the results obtained by x-ray and gastroscopy, and if so, to what extent?

4. What is the role played by the histologic structure and localization of gastric neoplasm in cytologic examination?

5. Is determination of the nuclear size of atypical cells useful in the assessment of the malignancy of the cytologic finding?

6. What importance is to be attributed to cell division as evidence of malignancy in exfoliative gastric cytology?

RESULTS

1 Chymotrypsin lavage

In all, a total of 782 lavages were performed on 721 patients using the chymotrypsin lavage method. The overall results are here presented first, and are followed by a separate more detailed analysis later

Results. Chymotrypsin lavage was performed on 138 patients of the *malignant group* in a total of 155 chymotrypsin lavages, and on 583 patients of the *non-malignant group* in a total of 627 chymotrypsin lavages. The results are given in Table 4 In the *malignant group* a finding cytologically suggestive of malignancy (malignant or suspicious) was obtained in over 80 per cent of both the total cases examined and of the cases verified operatively or by biopsy Of all the patients in the *malignant group* examined by the chymotrypsin method, a finding cytologically interpreted as malignant was obtained in 65 cases (47 per cent) and as suspicious in 47 cases (34 per cent) In 8 cases (6 per cent) the finding was inconclusive, and in 13 cases (9.5 per cent) it was negative. The cytologic study was unsuccessful in 5 cases (3.5 per cent) in 4 cases the smears failed, and in one case the neoplasm was located in the oesophagus.

In the *non-malignant group* the examination of one (0.2 per cent) of the 583 patients gave a false-malignant finding and the examinations of 10 (1 7 per cent) gave a false-suspicious finding. (These cases are described in detail on pp. 40-43) The cytological finding was inconclusive in 35 cases (6 per cent) and the smears were unsuccessful in 11 cases (1.9 per cent)

Table 4 Cytological reports on 721 cases studied by the chymotrypsin method

	Cases, total	Cytological finding				Technical failures
		malignant	suspicious	incon-clusive	negative	
[illegible]						
Operatively or bioptically	113	52 (46%)	40 (35.5%)	5 (4.5%)	11 (9.5%)	5 (4.5%)
Clinically	25	13	7	3	2	—
Malignant group, total	138	65 (47%)	47 (34%)	8 (6%)	13 (9.5%)	5 (3.5%)
Non-malignant group total	583	1 (0.2%)	10 (1.7%)	35 (6%)	526 (90.2%)	11 (1.9%)

patients who had often come from distant localities stay for examination after the diagnosis had been otherwise established. In addition, cytological examination was performed in 29 cases of bioptically (suction biopsy method) verified atrophic gastritis (Siurala and Seppälä 1960). Occasional patients with achlorhydria, pernicious anaemia or pernicious tape-worm anaemia were also examined. Few patients refused gastroscopy and cytological examination when it was suggested.

The series finally consisted of a total of 736 patients seen in 1957—59, all of whom had been examined clinically by gastric radiography and by gastric cytology, while in addition, gastroscopy had been performed on 582 patients. For subsequent treatment, the series was divided into the *malignant* and the *non-malignant group*. The grounds on which the division was effected are summarized in Table and will be described in detail later (pp. 28—30). The *malignant group* consisted of 151 patients with malignant neoplasm in the stomach or the distal part of the oesophagus, and the *non-malignant group* of 585 patients who during an observation period ranging from one year to three and a half years from the date of cytologic gastric examination were not found to suffer from such a neoplasm.

The majority of the patients in the present series were sent for cytologic examination by the Departments of Medicine University of Helsinki. Various other hospitals sent patients for gastroscopy to the Department of Endoscopy housed in the Second Department of Medicine a cytologic examination was performed at the same time.

Hospitals sending patients for gastric cytology were:

Out Patients Department of Medicine	476 patients
First Department of Medicine	107 "
Second Department of Medicine	110
Departments of Surgery	22
Helsinki Municipal Hospitals	14
Others	7 "
	736 patients

Distribution by sex and age. The *malignant group* of 151 consisted of 91 men and 60 women. If only those patients with a gastric neoplasm are included, the *malignant group* comprised 86 men and 56 women. Thus the male female ratio of patients with gastric neoplasm in the present series was 1.5 : 1. Of the 585 patients in the *non-malignant* group, 364 were men and 221 women, the ratio being 1.6 : 1. According to the data collected for their Cancer Registry by Saxén and Korpela (1958) the calculated male-female ratio for those who contracted gastric cancer during the year 1954 was 1.7 : 1, i.e. very close to that of the present series.

Appendix I compares the age distribution of the *malignant* and *non-malignant groups* and that of the *malignant group* with the age distribution of patients in Finland whose gastric neoplasm was diagnosed in 1954 (according to Saxén and Korpela, 1958).

Follow-up studies

Follow-up studies aimed to provide:

— further information about patients who were later examined at the Departments of Medicine,

Gastric lavage with Ringer's solution was performed on 7 patients, 5 of whom had gastric cancer The cytologic finding was malignant in three cases suspicious in one and negative in one. For 2 patients of the *non-malignant group* lavage revealed nothing indicative of malignancy

3 **False cytologic finding**

The finding in a cytologic study may be incorrect firstly if no cells indicative of malignancy are found in cancer and secondly if the cytologic finding is falsely interpreted as malignant in a patient not suffering from cancer If a cytologic examination is unsuccessful the result, in a way is also false.

In the present study cytologic examination of 29 patients of the *malignant group* yielded a false negative finding In 7 cases this was the result of a technically unsuccessful cytologic examination, in 8 cases the finding was inconclusive, and in 14 cases the finding was (falsely) negative. Of the patients in the *non-malignant group* the cytologic finding was falsely indicative of malignancy (malignant or suspicious) in 11 cases. These false cytologic findings are discussed in detail below

Unsuccessful examination. For 7 of the patients of the *malignant group* the cytologic examination was a failure. In 2 cases the negative finding can be explained by the fact that only oesophageal lavage was possible whereas the neoplasm was located in the stomach, while in a third case the patient underwent a gastric lavage and the neoplasm was located in th oesophagus. In 3 cases, the neoplasm was located in the antral part of the stomach, causing a partial stenosis of the antrum with subsequent retention which interfered with the examination. No re-examination was attempted, but biopsies taken during operations on these patients revealed scirrhous carcinoma in two and adenomatous carcinoma in the third. The seventh patient of this group had the neoplasm in the cardia of the stomach. The cytologic smears contained few cells, all of them squamous. Surgical exploration showed a crater like tumour the size of an egg adhering to the pancreas, the lymph nodes of varying size on both the larger and the lesser curvature and the omentum were interpreted as metastases. The patient died five months later No autopsy was performed but from the clinical picture and the operative finding the patient was considered to have died of gastric cancer

In the *non-malignant group* the cytologic examination failed 11 times (1 9 per cent)

Inconclusive cases. For 8 patients of the *malignant group* the cytologic finding was inconclusive. The diagnosis of a neoplasm was verified in 5 cases by a biopsy during operation and in one case by the autopsy findings. In the other 2 cases, the diagnosis was based on clinical examination and subsequent observation of the patients. Apart from one of the patients operated on, all of them died during the period of observation.

In 5 cases the cytologic preparations were unsuccessful. on two occasions the failure was the result of abundant debris caused by retention, while in 3 cases a large number of inflammatory cells covered a proportion of the exfoliated gastric cells. The smears from one patient were poor in cells. Yet since all the

The operations performed after gastric cytology were:

explorative laparotomy	in 30 cases
palliative surgery	9 "
partial gastrectomy	" 54 "
total gastrectomy	" 3 "
	total 96 cases

During the period of observation, an operation involving the abdominal cavity was performed on 119 patients of the *non-malignant group*. Partial gastrectomy was performed on 65 patients for gastric ulcer and on 6 for duodenal ulcer. Two patients underwent partial gastrectomy for a benign gastric neoplasm. In 19 cases either gastrostomy or explorative laparotomy was performed and two of these patients were found to have pancreatic carcinoma. Pyloric stenosis was the cause of pyloroplasty in two cases and of gastrectomy in one. One patient was operated on for diaphragmatic hernia, and 17 patients had the gall-bladder removed. Enterotomy was performed on 4 patients, one of whom was found to have carcinoma of the colon, one regional ileitis, in another part of the small intestine was resected because of an obstruction, and on the fourth an appendectomy was performed. Diseases of the reproductive organs led to one salpingectomy and one hysterectomy because of a myoma.

Fatalities. Additional information on those patients of the series who died was obtained by letters of inquiry and from the hospital case histories. The Vital Statistics Section of the Central Office of Statistics was consulted, the death certificates of all patients known to have died were checked and it was confirmed that patients who had failed to answer the letter of inquiry had not died.

To date 123 of the patients of the *malignant group* have died, an autopsy has been performed on 7.

Of the patients of the *non-malignant group* 40 have so far died, 4 of these patients had been operated on and an autopsy has been performed on 11. The causes of death in this group were:

neoplasms (not gastric)	14
cerebral vascular disorders	4
cardiovascular diseases	10
diseases of the alimentary canal	7
others	5
total	40 cases

Of the 14 cases who died from a malignant neoplasm other than a gastric one, 7 had a pulmonary growth, 2 pancreatic carcinoma, and 2 neoplasm of the bone system. One patient died of myeloid leucaemia, one of carcinoma of the colon, and one of ovarian carcinoma.

Clinical follow-up examination. Only a small percentage of the series provided sufficient follow-up data, spontaneously attending for the scheduled follow-up examination or consulting the clinic for some fresh disease. On receipt of a letter of inquiry many patients turned up at the clinic without any further prompting. Apart from a clinical examination, gastric radiology was performed if the patient had had abdominal trouble or if the previous examination had suggested a potential gastric neoplasm. In this way follow-up data were obtained on *119* patients of the *non-malignant group*. One of the patients

In the present series, the cytologic study failed in 4.6 per cent of all cases in the *malignant group* while the finding was inconclusive or negative for malignancy in 14.5 per cent. The reason for the failure was often the impurity of specimens, and since the majority of the series consisted of out patients, unsuccessful examinations or technical failures could not usually be repaired by a further examination. It was therefore often obligatory to pronounce on the preparations even though in some cases they were highly unsatisfactory. The information provided above (p. 37) on those patients of the *malignant group* subjected to a cytological re-examination suggests that such re-examination tended to reveal more gastric neoplasms. To ensure, therefore, that the results are as accurate as possible, all totally or partially unsuccessful examinations should be repeated, though even this may not suffice to guarantee that every case of gastric neoplasm may be diagnosed cytologically.

Ayabe and his colleagues have tried to assess how many neoplasms could be diagnosed cytologically. The cytologic report on a mucus specimen taken from the surface or in the vicinity of a gastric lesion during the gastrectomy of each of 168 patients was compared with a simultaneous biopsy specimen. Of these 168 patients, 83 suffered from carcinoma, and 78 of these (94 per cent) were correctly diagnosed on cytologic study. Two of the three negative cases represented a typical scirrhus without gross evidence of epithelial ulceration, and in the third case the staining was unsuccessful. In all the positive cases, cancer cells were easily found in the specimens taken from the vicinity of the ulceration, but in some of the specimens in which necrotic matter covered the surface of the ulcerating tumour it was difficult to find cancer cells even in smears taken straight from the lesion. Among the remaining 85 patients gastrectomized for a benign gastric lesion 83 gave specimens negative for malignancy while in 2 cases the finding was interpreted as suspicious. It seems, therefore, that gastric cytology will never reach 100 per cent diagnostic certainty.

Cytologically false-positive cases. In 11 cases the cytologic finding was suggestive of malignancy which later proved to be false or which to date at least has not been shown to be correct. In 10 cases the finding was listed as suspicious and in 1 case as malignant. The smears were once again studied microscopically and 9 of them were still classified as suspicious. Examples of false-suspicious cytologic findings are shown in Figs. 8-10. Details of the 11 cases are given below.

Case A. L. (No. 159/57) a railway worker of 54. Gastric x-ray revealed an ulcer located prepylorically. Gastroscopy showed two ulcerations in the region of the gastric angle, thought to be the result of erosive gastritis. Cytologic study revealed changes indicative of intestinal metaplasia but also showed small cell clusters that stained hyperchromatically as well as individual cells with slight nuclear changes of varying size and shape. The nucleoli were enlarged and the nuclear-cytoplasmic ratio was upset. The cytologic finding was interpreted as suspicious; the clinical diagnosis was gastric ulcer. A partial gastrectomy was

TECHNIQUE

Chymotrypsin lavage

The enzyme chymotrypsin lavage method developed by Rubin and Benditt (1955) was employed for collecting specimens for gastric cytology

Preparation of the patient. Prior to the examination the patient had to be without food overnight. If gastric emptying was impeded the patients in the clinic were kept on a liquid diet for a few days before the examination and the stomach was lavaged th night before In cases where gastric retention was known in advance or noticed at the outset of the examination, a gastric lavage to clean the stomach was performed before the chymotrypsin la age. Efforts were mad to avoid radiology with barium-containing contrast media for a minimum of three days before the cytologic examination. Before the actual examination the patients were given no premedication, nor was the pharynx anaesthetized For patients undergoing gastroscopy the cytological study was performed immediately after the gastroscopy Prior to gastroscopy these patients were given 40 mg papaverine hydrochlorid and 0.5 mg of methylscopolaminamine nitrate ("Skopyl" Pharmacia) subcutaneously and 100 mg of phenobarbital intramuscularly while local anaesthesia of the pharynx was effected by tetraca ne hydrochloride ("Pantocaine" 2 Hoechst) solution applied with a swab or pra and that of the oesophagus by lidocaine ("Xylocain viscous" 2 Astra solution.

Collection of samples. The patient was warned not to swallow saliva during the lavage Th gastric tube lubricated with water was introduced into the stomach through the mouth.

The stomach was emptied through the tube, then lavaged with Ringer s solution until the recovered fluid was lear The lavage specimen was set aside. For the chymotrypsin lav ge proper 7 mg hymotrypsin (Chymotrypsin caps. Armour were dissolved in 500 ml acetate buffer (0 1 molar acetate buffer was prepared by adding 13 6 g sodium acetate and 0.6 ml glacial acetic acid per 1 litre distilled water the pH of the buffer solution was 5.6) The freshly prepared solution was introduced through the tube into the stomach and left there for 10 minutes during which time the tube was kept sealed and the patient turned in decubitus 360 degrees The stomach was thereupon emptied quickly The last few drops, taken while the patient was in the left

gastric cancer was suspected but a laparotomy performed in the Department of Surgery revealed a superficial ulcer in process of healing, and no gastrectomy was found necessary. The biopsy specimen confirmed the gastric ulcer.

Case J. I. (No. 85/59), a woman of 62. Gastric x-ray revealed large coarse rugal folds and filling defect in the fornix taken to suggest the presence of tumour. Gastroscopy indicated tumour-forming gastritis, and the cytologic finding was suspicious for malignancy. The smears showed intestinal metaplasia, several cell clusters in which the nuclei were hyperchromatically stained and varied in size and shape, and a heavily vacuolized cytoplasm. Clinically the patient was thought to have gastric cancer but according to follow-up information year later the patient had undergone no operation and felt well.

Case E. V. (No. 111/59), a worker of 45. X-ray revealed large ulcer of the lesser curvature which was confirmed by gastroscopy though the finding could not with certainty be considered benign. Cytologic examination showed cells interpreted as suspicious: the smears contained a quantity of inflammatory cells and debris, but there were also several hyperchromatically stained clusters of cells with nuclei varying slightly in size, while the nucleoli were enlarged and their number had increased (Fig.9). The clinical diagnosis was gastric ulcer. No follow-up information has since been obtained on the patient personally but it is known that he has neither contracted, nor died of, gastric cancer during the observation period of something more than year.



Fig. 9.
Cytologically false suspicious finding. Case E.V 111/59

Case H. P. (No. 75/58), painter of 46. Gastric x-ray revealed region below the cardia which might have contained tumour. A blind area on the lesser curvature side interfered with gastroscopy but part from this nothing unusual was noted, except for slight gastritis. Cytologic study revealed cells suggestive of intestinal metaplasia and, in addition to ordinary cells of the surface epithelium, a large cluster of cells with particularly large-sized nuclei. The large nuclei were regular in shape but, because of the thickness of the smear their structure was not properly visible. The finding was classified as suspected malignancy but a second study might well reveal the cells as "P.A. cells". The patient underwent cholecystectomy in the Department of Surgery and no special findings were made in the stomach. According to follow-up information the patient felt well.

Case H. U. (No. 200/58) a tractor driver of 43. Gastric x-ray revealed large coarse rugal folds in the fundus, while gastroscopy showed only gastritic changes. The cytologic finding was suspicious: in addition to individual surface epithelial cells with highly vacuolized plasma, the smears contained small cluster of cells with nuclei of varying size and an increased number of nucleoli, while the vacuolized plasma showed no distinct cell borders. The clinical diagnosis was suspected gastric tumour. A follow-up examination two years later revealed that the patient felt well, and the gastric x-ray produced no remarkable findings. During the period of observation the patient had undergone no surgery.

Case K. T. (No. 187/57) lorry-driver of 46. Gastric x-ray revealed gastric ulcer but gastroscopy showed only gastritic changes. Cytologic study showed several clusters of cells with nuclear changes of varying size and shape and increased quantities of large nucleoli. No nuclear hyperchromatism was noted, however though the cytoplasm was vacuolized. The clinical diagnosis was gastric ulcer. At follow-up examination three years later he patient was well.

Case S. V. (No. 137/58), dock labourer of 58. Gastric x-ray suggested filling defect, but the examination was considered unsuccessful. Gastroscopy showed gastritic changes. The cytologic examination revealed cluster of few cells

them. A minimum of 4 slides was examined using a *low magnification* (10 × 10). Fig. 1 shows how hyperchromatic *malignant cells*, when screened on a low magnification, can be distinguished from the ordinary gastric surface epithelial cells. Higher magnifications and immersion oil (10 × 100) were used if required, for the study of individual cells or clusters of cells.

leucocytes or cellular debris, loss of distinct cell boundaries, and engulfment of one cell by another (cannibalism). The cytologic finding was interpreted as *malignant* if the specimens contained many single cells or large clusters of cells showing the most important criteria of malignancy outlined above, or displaying other additional signs of malignancy. The finding was interpreted as *suspicious* if the speci-

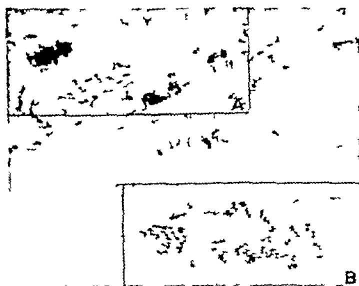


Fig. 1

Photomicrograph with lower magnification of cytological specimen; rectangle A contains many clusters of hyperchromatic malignant cells and rectangle B normal cluster of the surface epithelium. Case 224/59

In the present study, marked variation in size of nuclei, polymorphism and hyperchromatism of the nuclei, increased size or number of the nucleoli, and upset nuclear-cytoplasmic ratio were considered the *most important criteria indicating malignancy. Supplementary criteria indicating malignancy were*: irregularity of the chromatin net and thickening of the nuclear membrane, presence of mitotic figures and polynuclear cells, strong vacuolization of the cytoplasm and presence of cytoplasmic inclusions, such as pigment granules,

mens showed clusters of only a few cells or single cells conforming to the most important criteria for malignancy, or if changes otherwise noted did not indisputably suggest malignancy. The finding was classified *inconclusive* if it differed from the normal and from changes seen, e.g. in gastritis, but displayed few of the criteria suggesting malignancy. Pronouncements on the specimens included a description of benign features differing from the normal, and a comment to the effect that the finding was said to suggest,

reported a false malignant finding due to the misinterpretation of nasopharyngeal cells as malignant, in a case of lung cancer atypical cells had probably been swallowed with sputum, or had come off other smears during the staining process. These latter cells, known as "floaters" may be recognized by their more superficial position in relation to the general plane of the other cells in the smear. Garret et al. (1960) also warned against the possibility that malignant cells from somewhere other than the stomach might enter the lavage fluid during lavage. In the present series, gastric lavage produced a malignant cytologic finding in two cases of oesophageal carcinoma. According to Raskin and his co-workers (1958) healing gastric ulcers have been the most consistent source of atypical cells, and though such cells are not found in connection with all healing benign ulcers, a sufficient number have been encountered to warrant notice in gastric cytology. In Schade's study (1960) the false positive findings were due to the scaling off of cells in chronic atrophic gastritis.

In the present study malignancy was falsely suspected usually when the nuclei in a specimen appeared hyperchromatically stained and larger than usual at the same time as the cytoplasm was vacuolized and irregular. These are phenomena which resemble the cytologic changes in atrophic gastritis or a healing gastric ulcer and a finding of this kind, occasionally accompanied by pyknotic nuclear changes has therefore probably been responsible for most of the cases falsely suspected of malignancy.

P.A. cells were not falsely interpreted as suspicious except in one case in which the structure of the nuclei was not visible because of the thickness of the smear; the largeness of the nuclei provoked the false interpretation. If all the cases considered on cytology as suspicious could be re-examined cytologically the number of findings falsely suggesting malignancy might be still further reduced, but even as it is the reliability of the examination must be considered good in benign gastric complaints.

4. Comparison of findings on cytologic and x ray examination and on endoscopy

In the present study 736 patients were examined by gastric x-ray and 588 patients underwent endoscopy. The diagnostic results obtained by the different methods are now compared.

X ray examination and cytologic examination. In 84 of the 151 patients of the *malignant group* a finding correctly interpreted as gastric cancer was obtained by x-ray examination. In a further 42 cases the x-ray finding was suspicious, while in 6 cases the finding was inconclusive, and in 19 cases the x ray study revealed nothing suggestive of malignancy. Table 6 compares the findings on x-ray and cytological examination. Both methods often gave roughly the same number of malignant or suspicious findings.

The x ray findings for 9 of the 585 patients of the *non-malignant group* (1.5 per cent) were falsely interpreted as gastric cancer. The x-ray findings for 84 patients (14.4 per cent) were falsely suspected as malignant, and for 56 patients (9.6 per cent) the x-ray examination did not eliminate the possibility of

Cytological findings to illustrate the classification are shown in Figs. 2-5. In all photomicrographs using higher magnification a 10 μ line has been plotted to show the magnification used.

Re-examination. If the finding had been inconclusive or suspicious or if the smears had been unsuccessful the cytologic examination was repeated within two months of the first examination, unless other examinations made it unnecessary. A re-examination was in fact performed on 28 patients, while a cytologic re-examination was also performed in 23 cases where gastroscopy was renewed, regardless of the finding of the original cytologic examination. In all these cases the re-examination finding was entered in the final statement submitted on gastric cytology.

was due to the fact that the gastroscope could not be passed through the cardia or that visibility was inadequate even in the upper parts of the stomach. In 7 cases the gastroscopy was prevented by gastric retention or haemorrhage.

In 5 examinations (1 per cent) of patients in the *non-malignant group* the finding was falsely interpreted as malignant, and in 22 (4.5 per cent) it was falsely interpreted as suspicious. In the gastroscopy of 69 cases (15 per cent) either the possibility of malignancy could not be eliminated, or the examination was otherwise inconclusive. The gastroscopy of 13 patients (3 per cent) failed. In 357 cases (76.5 per cent) the gastroscopic finding was correct in that malignancy was not suspected at all.

Complementary value of the examination methods. Previous authors have not usually assessed the comparative diagnostic importance of these methods of examination. This is readily understandable since gastroscopy although a routine method of examination, is usually performed only when it may be expected to be of real use, and hence there exist few sufficiently large and comparable series in which the three examinations for gastric diagnosis — gastric x-ray gastroscopy and cytologic study — have been performed on identical patients. A fair comparison of the results is also impeded by the fact that the radiologist is provided with all the available medical history data to assist him in the correct interpretation of his findings; the gastroscopist is given the roentgenograms which already indicate the finding to be expected, the cytologist is also often provided with preliminary information on the cases to be studied. Rubin et al. (1953) showed that the three examination methods were complementary. When all methods, including endoscopy and the clinical findings, were combined, 109 of the 111 cases (42 malignant cases) were correctly diagnosed. Nieburgs and his co-workers (1960) tabulated comparatively the data on 91 gastroscopies, 93 cytologic studies and 122 roentgenographies; the percentages of correct diagnosis were 78 for gastroscopy 72.1 for roentgenography and 66.7 for cytology. The assessment of these results however is impeded by the fact that for the cytologic study they used Nieburgs abrasive brush method, and the examinations of no less than 29 patients were considered technical failures and excluded from the results reported. On the other hand the authors did not state whether unsuccessful gastroscopies had been eliminated, nor were the malignant and non-malignant cases distinguished. For these reasons, the reported results give no reliable picture of the complementary importance of the three examination methods. In a series of 68 patients (24 malignant cases) Burnett et al. (1960) showed that the combined use of radiology and gastroscopy provided a reliable diagnostic screening method. Exfoliative cytology revealed one early case of carcinoma of the stomach which the other methods could not have been expected to detect. They consider it therefore a valuable adjunct when the routine methods give negative results in clinically suspicious cases, though in their series the high incidence of false negative results (38 per cent) showed exfoliative cytology to be an unreliable

Partial gastrectomy had been performed on 13 patients before the cytologic study on 5 for a gastric neoplasm (the *malignant group*) and on 8 for a gastric ulcer (the *non-malignant group*). In these cases there were technical difficulties involved in a cytologic study since the gastric stump could usually contain little lavage solution, while the stomach emptied fairly rapidly with the result that the quantity of lavage fluid recovered was also small. Three of the 5 patients in the *malignant group* gave a cytologic finding indicative of malignancy one underwent a further operation for gastric reticulosarcoma, and an autopsy was performed on the third. No further operations, or autopsies, were performed on the one cytologically malignant case or the two cytologically negative cases. Examination of the 8 patients of the *non-malignant group* revealed nothing indicative of malignancy.

Results of re-examination. Cytologic re-examination was performed on 51 patients prior to the follow-up examination proper (the reasons for re-examination are stated on p. 35). In most cases, re-examination took place within a few weeks or at most two months of the first examination.

The results for 13 of the *malignant group* patients re-examined are given in Table 5. The degree of the cytologic malignancy of the findings increased on re-examination, whereas in the original examination the finding had been interpreted as negative or inconclusive in 10 cases and malignant or suspicious in 3 cases, the finding was now classified as malignant or suspicious in 10 cases and as negative or inconclusive in only 3 cases.

Of the *non-malignant group* 38 patients

Table 5. Comparison of findings on the original lavage and re-lavage in 51 cases (chymotrypsin lavage)

Group	Cases, total	Cytological finding: Malignant	Suspicious	Inconclusive	Negative
Malignant					
Original examination	13	1	2	8	2
Re-examination	13	3	7	2	1
Non-malignant					
Original examination	38	—	1	11	26
Re-examination	38	—	2	3	33

were re-examined. In the original examination, the cytologic finding was negative in 26 cases, inconclusive in 11 cases, and suspectedly false positive in one. Re-examination gave a cytologic finding which was negative in 33 cases, inconclusive in 3 cases, and suspectedly false positive in 2 cases. The case originally believed suspicious was false suspicious on re-examination also.

2. Ringer lavage

A cytologic study using Ringer's solution alone was made on 15 patients.

An *oesophageal lavage* with Ringer's solution was performed on 8 patients because the tube could not be passed all the way to the stomach. Six patients had oesophageal carcinoma, the cytologic finding was interpreted as malignant in five and as suspicious in one case. The remaining two patients had gastric carcinoma but there was no cytologic indication of malignancy.

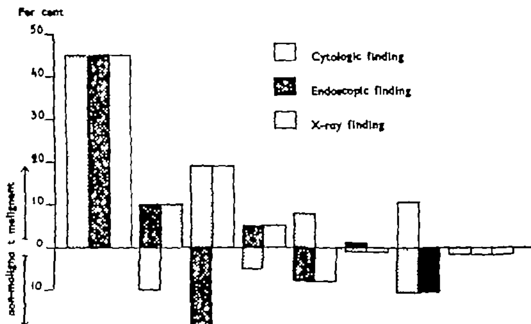


Fig. 11

Complementary value of x-ray endoscopic and cytologic examinations in 124 cases of cancer of the stomach and the distal part of the oesophagus.

Comment. X-ray examination is undoubtedly the most appropriate method of examination for gastric diagnosis. By its means, it is possible to demonstrate, or direct well-founded suspicion to 60—90 per cent of the gastric neoplasms in patients whose symptoms call for gastric x-ray study (e.g. Templeton 1955 Kettunen 1956). Some of the gastric neoplasms, however particularly in their early stages, escape detection by roentgenology. Furthermore, gastric x-ray examination may also yield findings falsely indicative of gastric cancer and supplementary methods are therefore required to confirm the diagnosis. This emerged clearly in the present study of a series in which, as a result of the indications for examination which were employed, 25 per cent of the *non-malignant* group gave an x-ray finding which either suggested or did not eliminate the possibility of, a gastric neoplasm. Endoscopy has been the usual supplementary method of examination in inconclusive cases, but, as can be seen from the unselected series subjected to endoscopic examination, many patients are not suited to this kind of examination, and not even successful examinations always eliminate the possibility of malignancy. The high percentage of unsuccessful gastroscopies in the *malignant group* of the present series (23 per cent) resulted from the fact that patients were sent for this examination without advance screening by the

smears showed individual hyperchromatic cells, believed to be gastric epithelial cells the specimens could not be considered total failures or negative even though they were not to be taken as conclusively indicative of malignancy

The finding for 35 patients (6 per cent) of the *non-malignant* group was inconclusive

Negative cases. A finding negative for malignancy was obtained for 14 patients of the *malignant group* Later microscopic study of preparations not previously examined showed suspicious cells in three cases. Of the remaining 11 cases malignancy was verified histologically in 7 and clinically in 4 The neoplasm was discovered in the antrum in 3 patients and had spread over a large area of the stomach in 4 patients. Two patients were examined following subtotal gastrectomy for cancer but in the last 2 cases the site of the neoplasm was not known with certainty The negative cytologic findings may be partly explained by the fact that in the cases of widespread or antral neoplasm the stomach contained retention fluid which interfered with the cytologic study The smears of such patients contained a considerable quantity of debris but since they also showed cells of the gastric surface epithelium they could not be classified as failures. In one case of leiomyosarcoma in the antrum, the neoplasm was found, on operation, to be completely in the submucosa, and a finding indicative of malignancy was not therefore to be expected.

Comment. Several factors may be responsible for a failure or negative finding in cytologic studies of cancer Among these factors may be listed technically unsatisfactory preparations gastric retention, overlooked cancer cells, intramural tumours, necrosis in large tumours, and ulcer craters covered with necrotic membranes (e.g Graham et al. 1948 Swarts et al. 1950 Seybolt et al. 1951 Lemon 1952, Traut et al. 1952, Cooper and Papanicolaou 1953 and Rubin et al. 1953) The purity of the preparations seems to be of the utmost importance for a successful cytologic examination, a fact that is specifically emphasized in the paper by Ayabe, Ota and Izaki (1954) These authors declared that there were frequent unclean specimens with many foreign elements or strongly degenerated cells which prevented the detection of cancer cells. Diagnostic accuracy was 92 per cent in cancer cases with clean smear specimens, while with unclean specimens it was only 17 per cent. Ayabe et al. attributed unclean specimens to (1) disturbance of the gastric lavage process, (2) pyloric stenosis and (3) digestion by the gastric juice. In their cases without pyloric stenosis, 83 per cent of the specimens acquired were clean and the cytologic finding indicated malignancy in 82 per cent of them. In the cases with pyloric stenosis 36 per cent of the specimens obtained were clean, and the cytologic finding was positive in 47 per cent. Ayabe and his co-workers also found that the cleanliness of specimens of all cases except those with pyloric stenosis depended on the acidity of the gastric juice and that in cases with high free acidity the smears were more frequently unclean.

the reason why cytologic examination does not always lead to a correct diagnosis in such cases as these (e.g. Wollum et al. 1952, Hecht and Cohen 1953, Rubin et al. 1953, Grimes et al. 1954). Scirrhous carcinoma, however, can often be detected by cytologic study. Umiker et al. (1958) reported that cytologic study gave each of the 11 scirrhous carcinomas of their series a positive finding, though admittedly a further 5 scirrhous carcinomas yielded unsatisfactory specimens. According to these authors it was significant that the scirrhous carcinomas, *though they showed no gross evidence of surface involvement*, were found to involve the mucosal surface in microscopic sections. The mucoid carcinoma, which is in fact considerably less common than the ordinary adenocarcinoma, also seems to escape cytologic detection. Hecht and Cohen (1953), for example, considered it difficult to make a diagnosis in mucoid carcinoma, though Seybolt et al. (1951) had obtained a finding indicative of malignancy in 3 of the 6 mucoid carcinomas of their series.

The results of cytologic study are also *affected by the degree of differentiation* of the neoplasm. In mucoid carcinoma the interpretation of the cytologic finding may be dificult even with more advanced differentiation, although interpretation is usually easier than for carcinomas of little differentiation. Umiker et [illegible]) held the opinion that ana[illegible] nant cells were either less [illegible] more easily overlooked, for only [illegible] undifferentiated form [illegible] positive smears [illegible] (19[illegible] considered anap[illegible] a [illegible] tologic failure [illegible]

are usually more friable than are more mature cancers, it may be assumed that the decreased accuracy for this group is the result of greater difficulty of recognition rather than of a lower rate of exfoliation.

In the present series the correlation of cytologic results to the histologic type of the neoplasm was examined by classifying the series according to the histologic structure of the neoplasm. The classification adopted was that recommended by the committee appointed by Unio Internationalis Contra Cancrum (1958). The *classification demanded a degree of ruthlessness*, since a single section may often display, for example, highly anaplastic tumour cells side by side with distinctly differentiated cells. For the sake of clarity, however, the series was classified according to the dominating tumour tissue type, ignoring any additional features present. The adenocarcinoma group, the biggest group of all, contains the cases in which the biopsy specimens showed distinct glandular structure. The scirrhous carcinoma group includes the neoplasms whose histologic picture was *characterized by a profusion of stroma*. The medullary cancer group consists of cases in which the biopsy specimens showed little stroma but many tumour cells. The solid carcinoma group includes the cases in which the tumour is composed of solid epitheli[illegible] ls. In the present material it was [illegible] a rule possible to draw conclu[illegible] the histological [illegible] of the ne[illegible] the basis of the [illegible] ologic spec[illegible] cases a [illegible] ection [illegible] made [illegible] ually [illegible] d [illegible] 7) and [illegible] e.g.

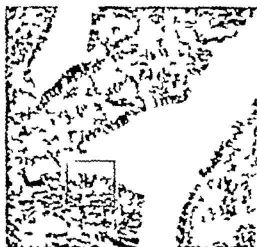


Fig. 6.



Fig. 7

Fig. 6. Photomicrograph with lower magnification of biopsy specimen shows on the right normal surface epithelium and on the left local dysplastic proliferation in the surface epithelium. Case A.L., 159/57

Fig. 7. Photomicrograph with higher magnification shows in the rectangle of Fig. 6 nuclear irregularity, nuclear prominence and mitotic figure (indicated by the arrows)

performed in the Department of Surgery. The biopsy specimen revealed an ulcer with local dysplastic proliferation in the surface epithelium. The histologic findings are shown in Fig. 6 and 7.

The patient died at home 8 months after examination. He was considered to have died of cardiac failure due to arteriosclerosis.

Case K.L. (No. 121/57), an ex-farmer of 73. From the x-ray the stomach seemed small and deformed, and two ulcers were suspected. Gastroscopy revealed only atrophic mucosal changes. The cytologic finding was classified as suspicious but on further microscopic study was altered to inconclusive. Smears taken contained a large quantity of gastric cell clusters and blood. The nuclei were hyperchromatic, polymorphic and varying in size, the nucleoli had increased, and the nuclear-cytoplasmic ratio was upset. The clinical diagnosis was suspected gastric carcinoma. On surgical exploration in the Department of Surgery and cholecystectomy nothing special was noted in the stomach. The patient died less than two years after the examination, evidently of coronary occlusion.

Case B.E. (No. 105/59), a woman of 58. Gastric x-ray revealed a narrow and stiffened prepyloric part, which was considered a possible indication of malignancy. Gastroscopy showed deformation of the gastric angle and of the antrum, which was also considered suspicious. The cytologic study of fasting specimen showed a cluster of cells considered as suspicious; the nuclei varied slightly in size but were hyperchromatic, while the nucleoli were enlarged and numerous though the nuclear-cytoplasmic ratio was normal (Fig. 8). Clinically



Fig. 8.

Cytologically false suspicious finding. Case B.E., 105/59

Fig. 14

Cytologically malignant cells. Bioptically medullary carcinoma. Case 303/58.

Fig. 15

Malignant cells with single mitosis. Bioptically solid carcinoma. Case 14/59

Table 9. Cytologic findings in 101 gastric neoplasms and 4 neoplasms of the distal part of the oesophagus classified according to histologic type

Histologic type of neoplasm	Cases, total	Cytologic finding				Technical failures
		Malignant	Suspicious	Inconclusive	Negative	
Adenocarcinoma	49	27	16	2	3	1
Scirrhous carcinoma	13	3	6	2	—	2
Medullary carcinoma	11	6	3	1	1	—
Solid carcinoma	17	6	9	—	2	—
Mucoid carcinoma	4	1	3	—	—	—
Papillomatous carcinoma	1		1	—	—	—
Epidermoid carcinoma	4	2	1	—	—	1
Lymphoma malignum	3	2		1	—	—
Leiomyosarcoma	1			—	1	—
Histologic type not known	2		1	—	1	—

with no distinct cell borders and with vacuolized plasma. The nuclei were noticeably differen in size and shape, and though the nucleoli were not large, they had increased in number. The finding was classified as suspectedly malignant (Fig. 10). The clinical diagnosis as achylia gastrica. No personal follow-up information was obtained on the patient but from other sources appears that he has neither contracted, nor died of, gastric cancer during the observation period of over two years.

Case T. J. (No 179/57) plumber of 51. Gastric -ray and gastroscopy revealed medium-sized ulcer. Cytologic study showed clusters of cells with hyperchromatic polymorphic nuclei of varying size. The nucleoli were enlarged and more numerous. The vacuolized cytoplasm included leucocytes, and the finding was classified as suspicious. The clinical diagnosis was gastric ulcer. The patient underwent gastrectomy at the Department of Surgery. Biopsy finding: gastric ulcer. At follow-up examination two years later the patient was well.

Case I. I. (No 175/57) farmer of 41. Gastric -ray showed gastric ulcer and gastroscopy revealed deformed gastric angle but only part of the ulcer. In the cytologic study the smears contained considerable quantities of blood, as well as several cell clusters first interpreted as malignant, since the nuclei were hyperchromatic though without definite differences in size and shape. The nucleoli were large and more numerous. The nuclear-cytoplasmic ratio was upset, and the cellular borders had disappeared. On microscopic re-examination the finding was classified as inconclusive. The clinical diagnosis was gastric ulcer. On laparotomy no gastrectomy was considered necessary since only cicatrization was seen in the stomach. Biopsies of the lymph nodes revealed nothing suggestive of malignancy. No personal follow-up information has been obtained on the patient but from other sources it appears that he has neither contracted, nor died of, gastric cancer during the observation period of over three years.

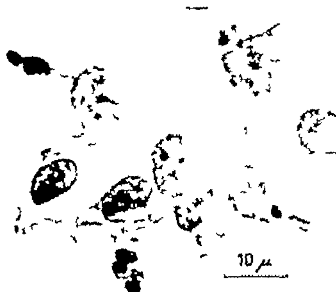


Fig. 10

Cytologically false suspicious finding. Case S.V. 137/58.

A cytologic finding falsely suggestive of malignancy may be attributed to several factors. In the study by Rubin and his co-workers (1953) for example, a false suspicion of malignancy arose from the interpretation of the so-called "P.A. cells" and active macrophages as malignant. Seybolt, Papanicolaou and Cooper (1951) in their paper on gastric cytology

a total of 118 patients with gastric neoplasms not subjected to surgery prior to the gastric x-ray gastroscopy and cytologic examination. The site of the neoplasm was determined from operative information on the spread of the tumour or where no surgery was performed, on the basis of concurrent x-ray and endoscopic findings. It may sometimes be difficult to determine the site of a neoplasm — if, for example, the neoplasm has spread widely In 16 of the present cases the neoplasm was so widespread that the origin of the tumour could not be identified, and these cases are listed separately In a further 6 cases, no reliable site for the neoplasm was ascertained. In 96 cases, however the precise position could be determined, the neoplasm was in the cardia or fornix in 13 cases (12.5 per cent) in the body in 36 cases (37.5 per cent) and in the antrum in 47 cases (49 per cent) The percentage of sites in the cardia and fornix (12.5) is perhaps too high compared with those elsewhere in the stomach, but this results from the fact that neoplasms which had spread widely beyond the area could be considered as primarily situated in the region of the cardia or fornix, while neoplasms infiltrating well into the body and antrum could not be conclusively localized in either but had to be classified among the widespread neoplasms.

To assess the significance of the site of neoplasms, a comparison of findings obtained by the different methods (gastric x-ray gastroscopic, cytologic examination) is given in Table 10 in which the 118 gastric neoplasms are classified according to site Of 13 neoplasms situated in the cardia a finding indicative of malignancy was obtained cytologically in 9 cases, by x ray in 8, and by gastroscopy in 2. The poor gastroscopy result is partly explained by the fact that a neoplasm in the cardia is often in the blind area since the gastroscope cannot be passed into the stomach. For this reason, gastroscopy failed in 8 of the 13 cases in which the neoplasms were situated in the cardia or the fornix. On the other hand, some authors consider the gastroscopic finding as indicative of malignancy if the gastroscope cannot be passed through the cardia (e.g., Benedict 1949 Schindler 1950 and Lehtonen et al. 1960) In the present series, the neoplasms in the region of the body were best diagnosed by cytologic examination, which gave a finding indi-

Table 10. The results of x-ray gastroscopic and cytolog

Site of neoplasm	Cases, total	X-ray examination			
		malignant	suspicious	inconclusive	negative
Cardia and fundus	13 (11)	7	1	2	3
Body	36 (30.5)	16	12	—	8
Antrum	47 40*	23	18	3	1
Widespread	16 13.5	11	5	—	—
Not known	6 5	1	1	—	4
Total	118 100*	60 (31)	3 (31)	5 (4*)	16 (14)

Table 6. Findings on gastric x-ray and cytologic examination in the 151 patients of the malignant group.

	Cases, total	Finding				Technical failures
		Malignant	Suspicious	Inconclusive	Negative	
Gastric x-ray	151	84 (55.5%)	42 (28%)	6 (4%)	19 (12.5%)	— —
Cytologic study	151	73 (48%)	49 (32.5%)	8 (5.5%)	14 (9%)	7 (5%)

malignancy. In 436 cases (74.5 per cent) the x-ray finding was correct in that no indication of malignancy was given. In the *non-malignant group* a finding falsely suggestive of malignancy was obtained definitely more frequently by x-ray examination than by cytologic examination, though this was the result, in part at least, of the indications according to which patients were selected for the examination.

Endoscopy and cytologic examination. Oesophagoscopy was performed in 4 cases of oesophageal neoplasm, with findings suggestive of malignancy in all, and in two cases of carcinoma of the cardia in one of which a neoplasm was noted while in the other it was not. The gastroscopies were performed in the Second Department of Medicine and were, with few exceptions, attended by the writer. In all, gastroscopy was performed on 118 patients of the *malignant* and 466 of the *non-malignant group*; the equipment used was either Wolf-Schindler's standard gastroscope or Taylor's flexible gastroscope. The results of these examinations are given in Table 7 which also shows the results of the x-ray and cytologic examinations. A finding correctly interpreted as malignant was obtained in 45 cases (38 per cent) and a suspicious finding in 25 cases (21 per cent). In 12 cases (10 per cent) the gastroscopic finding was inconclusive and in 9 cases (8 per cent) negative for malignancy. The examination was unsuccessful in 27 cases (23 per cent). In 20 cases the failure

Table 7. The findings on gastroscopy, x-ray examination and cytologic examination of 118 patients of the malignant group and 466 of the non-malignant group.

	Cases, total	Finding				Technical failures
		Malignant	Suspicious	Inconclusive	Negative	
Malignant group						
Gastroscopy	118	45 (38%)	25 (21%)	12 (10%)	9 (8 %)	27 (23%)
X-ray	118	60 (51%)	37 (31%)	5 (4%)	16 (14%)	— —
Cytology	118	53 (45%)	42 (35.5%)	7 (6%)	10 (8.5%)	6 (5%)
Non-malignant group						
Gastroscopy	466	5 (1%)	22 (4.5%)	69 (15%)	357 (76.5%)	13 (3%)
X-ray	466	8 (2%)	76 (16%)	47 (10%)	335 (72%)	— —
Cytology	466	1 (0.2%)	10 (2%)	29 (6%)	418 (90%)	8 (1.8%)

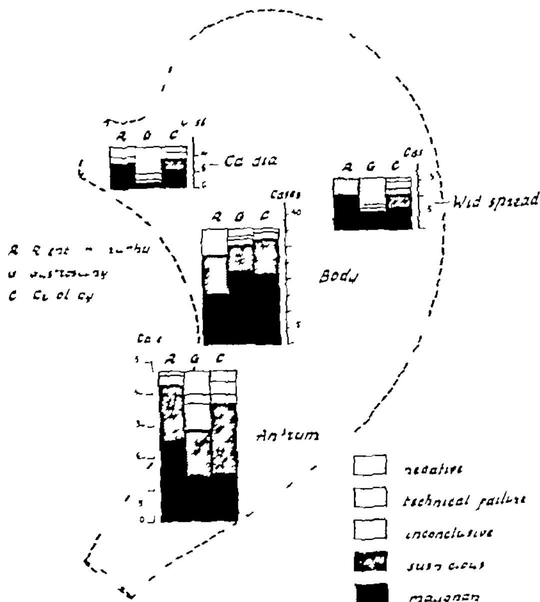


Fig. 16.
Findings obtained by X-ray, gastroscopic and cytologic examinations in 118 gastric cancers classified according to site.

logy and x ray examinations seem to yield similar results.

6. The nuclear size of exfoliated cell

The presence of cells with giant nuclei and the occurrence of variations in nuclear size in cytologic smears, are considered important signs of malignancy. Previous investigations, however have paid little attention to the measurement of cellular or nuclear size in gastric cytology specimens, though Marini (1909) studied the

screening test for carcinoma of the stomach.

In an earlier paper the writer in collaboration with Lehtinen et al. (1960) suggested that gastroscopy and cytologic study were appropriate methods of supplementing x-ray examination. This suggestion is borne out in the present, more extensive series. In 102 of the 124 cases of the *malignant group* in which all three examinations — x-ray, endoscopic and cytologic — were performed a roentgenological finding indicative of malignancy (malignant or suspicious) was obtained. Of the remaining 22 cases, in which the gastric x-ray gave a negative finding for malignancy, a finding indicative of malignancy was obtained in 20 cases either by gastroscopy or cytologic study. Only 2 cases showed nothing indicative of malignancy but re-examination by x-ray one month later gave a finding suggestive of malignancy in one of them. In the other it was not certain that a gastric neoplasm existed at the moment of examination, the patient had previously been gastrectomized for cancer but a cytologic examination was made only after the operation, and nothing indicative of ecidivation was noted in the gastric stump. The patient died 9 months after these examinations. His death was attributed to a metastatic gastric carcinoma but he underwent no re-operation after the examinations, nor was an autopsy performed. Table 8 gives the findings on gastroscopy and cytologic study of 22 cases of the *malignant group* in which the x-ray examination was negative for malignancy.

It is evident from the foregoing that none of the methods of examination employed sufficed to diagnose every neoplasm, and the x-ray, endoscopic and cytologic examinations of many patients of the malignant group gave a finding which was either negative or inconclusive so far as malignancy was concerned. For 56 of the 124 patients (45 per cent) of the malignant group that were subjected to all three methods of examination, the finding was indicative of malignancy (malignant or suspicious) on each examination. Both x-ray and cytologic finding indicated malignancy in 24 cases (19 per cent) and both x-ray and endoscopic finding in 12 cases (10 per cent). Both endoscopic and cytologic examination gave a finding indicating malignancy in 6 cases (5 per cent) while the x-ray finding in these cases was negative or inconclusive. X-ray examination alone indicated malignancy in 10 cases (8 per cent) and cytologic examination alone in 13 (10.5 per cent). Gastroscopy alone suggested malignancy in one case (1 per cent). In 2 cases, the finding by all three methods was negative. Fig. 11 shows the complementary value of the findings obtained by the different methods of examination.

Table 8. Findings on endoscopic and cytologic examination of 22 patients of the malignant group in which the x-ray examination was negative for malignancy

	Finding				
	Malignant	Suspicious	Inconclusive	Negative	Technical failure
Gastroscopy	3	4	7	5	3
Cytology	9	10	1	2	—

Table 11 Distribution of the cases in which nuclear size was measured.

Histologic structure	Total studied		Type of cell studied
	Biopsy specimens	Cytologic specimens	
Normal	6		Surface epithelium in body region, and glandular cells.
Normal	8		Surface epithelium of the pyloric region and glandular cells
Atrophic gastritis	7 (6)		Surface epithelium Pseudopyloric glands
Atrophic gastritis in pernicious anaemia patients	6		Metaplastic changes
Gastric ulcer	6	5	Surface epithelium and metaplastic changes
Not known		8	P A. cells of the cytologic specimens
Gastric carcinoma	37	19	Tumour tissue cells Atypical and anaplastic cells
Total cases	70	32	

a cytological examination was made of 7 atrophic gastritis and 4 gastric ulcer patients. In the *malignant group* the nuclei of 37 gastric cancers were measured from biopsy specimens and those of 19 of the 37 from cytologic smears also.

Statistical methods These measurements were treated statistically and for this purpose the series was divided into different groups. In comparing the groups, the observations for each group x^ν are assumed to have the same standard deviation σ which was estimated as follows:

$$\sigma = \sqrt{\frac{\sum_{\nu=1}^{k} n \; s^2}{\sum_{\nu=1}^{k} (n - 1)}},$$

where k is the number of groups to be compared (the value 1 of k gives separately the standard deviation of each single group) n the number of observations in the νth group and s^2 the variance of νth group. If $\bar{x}$ is the mean value of the νth group

$$s^2 = \frac{1}{n_\nu} \sum_{=1}^{n} (x^\nu - \bar{x})^2$$

The groups have been compared in pairs by means of the variable

$$y = \frac{\bar{x}_{\nu_1} - \bar{x}_{\nu_2}}{\sigma \sqrt{\frac{1}{n_{\nu_1}} + \frac{1}{n_{\nu_2}}}},$$

which has been simply assumed to follow the normal distribution.

In some frequency comparisons the standard deviation has been given the value

$$\sigma = \sqrt{f \, (1 - f)}$$

where f is the mean frequency in the groups compared

The degree of statistical significance is expressed as ε, the value of which indicates the degree of probability with which the observed difference is due to chance alone. $\varepsilon = 0.001$ designates a highly significant difference between the groups, $\varepsilon = 0.01$ a significant difference, and $\varepsilon = 0.05$ an almost significant difference.

gastroscopist. Consequently gastroscopy was performed in cases where a successful result was prejudiced n advance by the x-ray f nding The failures were mostly due to nability to pass the gastroscope th ough the cardia or to inadequate vi ibility inside the tomach Even an unsuccessful examinat on, however may pr ve a useful diagnostic aid since th arresting of the gastrosc pe n the cardia may n tself be considered an nd cation of malignancy

The results obtained on hymotrypsin la age concu with those eported in th l terature see pp 18 14 For gastric neopla ms, cytologic study proved tself a d gnostic method as reliabl as x y examination Had the unsuc essful and the inconclus ve cytologic exam nations been epeated the cytologic tudy might ha yielded even better esults than th eported This is suggested by the fa t that in those cases of th *malignant* g n which the cytologic examination w epeated the number of uspected malignancies usually ncreased. In the p esent series, cytologic study produced uspi ious finding in on case which on ubsequent surgery proved to be ca ci n ma in situ. In 13 cases of gastric neoplasm 10 5 per cent classified as negative by the ther examinations the cytologic examination gave a malignant or suspicious finding A finding falsely suggest ng malignancy was obtained in only 11 ases (2 per cent of the *non-malignant* up This concurs w th the published sults for various methods of gastric cytology ccording to which the incidence of ses falsely interpreted as malignant is less h n 2 per cent in the best series and that f falsely suspected cases under 5 per cent.

On the basis of these results t must be concluded that, although the examination is time-consuming and trained workers are essential for the interpretation of the findings cytologic study is well adapted for use a a supplementary examination method n gastric diagnosis

5 The significance of the histologic type and the site of the neoplasm

Histologic type It is often difficult t determine the histologic type of gastric cancer Sinc cytologic study is the investig tion of the microscopic structur of the individual cell and cell clusters recovered t is of pecial interest to compa e th cytologic esults for histologically different types of neoplasm Few attempts ha e been made to correlate the cyt logical content of smears with the histological sections of pa ent tissue taken f om specimens after operation. Schade 1959 who has made some contribution to this basic task, considered t quit mpossible when dealing w th gastric cytological specimens to predict the tumour type

Accord ng to Seybolt, P panicolaou and Cooper (1951 the pathologic type of tumour seemed to have a considerabl ffect on the chances of obtaining a positiv smear Using the conventional aspiration method they found that in over a half of the 134 adenocarcinomas of their series the cytologic finding indicated suspected malignancy The result, how ever was poorer n scirrhous carcinoma only one out of a total of 14 cases was indicated cytologically Scirrhous carcinoma usually grows by infiltration under the mucosa, rarely involving the mucosa itself, and many authors accept this as

Table 13 The mean nuclear dimension f gastric surface epithelium or glandular cells in total of 33 biopsy specimens from normal subjects and patients with non-malignant gastric complaints

	Cases								Means
NORMAL SUBJECTS									
Body region									
Surface epithelium 6 cases	1	2	3	4	5	6			
Mean value of uclear dimension	5.7	5.2	5.1	5.5	5.4	5.8			5.45
Variance	1.0	1.5	0.7	0.8	0.6	0.7			0.88
Chief cells 6 cases	1	2	3	4	5	6			
Mean value of nuclear dimension	4.4	5.1	4.5	4.3	4.8	4.9			4.67
Variance	0.3	0.4	0.4	0.3	0.4	0.3			0.35
Parietal cells 6 cases	1	2	3	4	5	6			
Mean value of nuclear dimension	5.5	6.2	5.6	5.4	6.0	5.6			5.72
Variance	0.3	0.4	0.4	0.4	0.4	0.2			0.35
Mucous neck cells 6 cases	1	2	3	4	5	6			
Mean value of nuclear dimension	5.5	5.4	4.9	5.3	5.8	6.2			5.52
Variance	1.7	0.6	0.5	0.9	1.2	0.5			0.90
Pyloric region									
Surface epithelium 8 cases	7	8	9	10	11	12	13	14	
Mean value of uclear dimension	6.6	5.0	6.3	5.8	6.5	6.2	6.6	6.7	6.21
Variance	1.2	0.6	1.7	0.6	0.7	0.7	0.9	0.8	0.90
Pyloric glands 8 cases	7	8	9	10	11	12	13	14	
Mean value of nuclear dimension	5.9	5.1	6.1	6.4	6.5	5.6	5.3	5.5	5.80
Variance	0.7	0.6	0.7	0.7	1.0	1.2	0.5	0.6	0.75
ATROPHIC GASTRITIS PATIENTS									
Surface epithelium 7 cases	15	16	17	18	19	20	21		
Mean value of nuclear dimension	6.6	6.6	6.1	5.1	5.4	6.2	7.0		6.14
Variance	1.0	1.0	0.6	0.5	0.6	0.5	1.2		0.77
Pseudopyloric glands 6 cases	15	16	17	18	19	20			
Mean value of nuclear dimension	6.0	5.2	5.8	5.4	5.9	6.2			5.75
Variance	0.6	0.9	0.9	0.4	0.8	0.8			0.73
PERNICIOUS ANAEMIA PATIENTS									
Epithelial metaplasia 6 cases	22	23	24	25	26	27			
Mean value of nuclear dimension	6.5	7.8	7.0	6.8	7.2	7.0			7.05
Variance	1.1	1.0	1.1	0.6	0.9	1.5			1.03
GASTRIC ULCER PATIENTS									
Surface epithelium or metaplasia 6 cases	28	29	30	31	32	33			
Mean value of nuclear dimension	6.1	6.0	7.6	6.8	7.9	7.1			6.9
Variance	0.6	0.8	1.0	1.0	0.7	0.6			0.78



Fig. 12
Cytologically suspicious cells, suggesting epidermoid carcinoma. Bioptically epidermoid carcinoma. Case 124/59



Fig. 13.
Cytologically malignant cells. Bioptically adenocarcinoma. Case 217/58.

adenocarcinomas (Fig. 13) but the malignant lymphomas of the material for instance, were not diagnosed cytologically: they gave a finding either suggestive of malignancy (Fig. 18) or inconclusive. Nor was it possible to say on the basis of the cytological finding whether a patient had a scirrhous or solid carcinoma (Fig. 15). A few cytologic findings suggested a medullary carcinoma (Fig. 14).

Table 9 shows the cytologic findings, classified according to the histologic type of the neoplasm, for 105 patients of the *malignant group*. Cytologic study produced a finding indicative of malignancy in 88 per cent of the adenocarcinomas, in 9 of the 13 scirrhous carcinomas, in 9 of



Fig. 18.
Two giant nuclear cells; the nuclear dimension of the larger cell was 22 μ. Bioptically reticulosarcoma. Case 272/58.

neoplasm, the mean nuclear size could vary distinctly even in cases of the same histologic type (Appendix 3)

The significance of nuclear size as a criterion for malignancy was studied by determining, from the non-malignant cases of the series, the dimension of the largest nucleus that was not a cancer cell nor a "P. A. cell" ("P. A. cells are disregarded in the following: they are usually easily recognized, and since they are macronuclear cells their inclusion would raise the maximum nuclear size of the non-malignant cells so high that the measuring procedure would serve no practical purpose)

The dimension of the biggest nucleus in a cell which was neither a cancer cell nor a P. A. cell was determined mathematically thus, the distribution of the mean dimensions x_ν of the biggest nuclei found in the biopsy specimens of *non-malignant* cases (pernicious anaemia and gastric ulcer) was studied together with the distribution of the variances s of nuclear dimensions. From these, the upper limits r_1 and r_2, as accurate as possible, were determined, according to the normal distribution for the theoretical mean values $m(\bar{x}_\nu)$ and $m(s^2_\nu)$ using the empirical mean values $\bar{x}$ and $\bar{s}^2$ and the standard deviations

$$\sigma(\bar{x}) = \sqrt{\frac{1}{N-1}\sum_{\nu=1}^{N}(\bar{x}_\nu - \bar{x})^2}$$

and

$$\sigma(s^2_\nu) = \sqrt{\frac{1}{N-1}\sum_{\nu=1}^{N}(s^2_\nu - \bar{s}^2)^2},$$

where N is the total of $\bar{x}_\nu$ and s^2_ν.

At the same time r_2 was taken to be the upper limit of the standard deviation square σ^2 of the nuclear distribution for every person — in other words, it was taken for granted that every patient's nuclear distribution had the same standard deviation $\sigma = \sqrt{m(s^2)}$

Subsequently the upper limit r_3 as accurate as possible, was determined for the mean values $\bar{x}_\nu$ themselves from the mean value r_1 and the standard deviation $\sigma(\bar{x}_\nu)$ of $\bar{x}$ values and assuming the normal distribution. At the same time r_3 was taken as the upper limit of the theoretical mean values m of nuclear distributions.

Finally on the basis of the mean value r_3 and the standard deviation $\sqrt{r_2}$ and assuming the normal distribution the upper limit r of the nuclear dimension x^ν itself was determined.

The probabilities obtained in determining the limits r_1, r_2, r_3 and r_4 are:

$$P\,(m\,(\bar{x}_\nu) > r_1) = \varepsilon_1$$

$$P\,(\sigma^2 > r_2) = \varepsilon_2$$

$$P\,(m_\nu > r_3 \mid m\,(\bar{x}_\nu) = r_1) = \varepsilon$$

$$P\,(x^\nu_\nu > r_4 \mid \begin{smallmatrix} m_\nu = r_3 \\ \sigma = \sqrt{r_2} \end{smallmatrix}) = \varepsilon_4$$

the 11 medullary carcinomas, and in 14 of the 1 solid carcinomas. Other types of neoplasm were less numerous in the present series, but *cytologic study indicated malignancy* in all of the 4 mucoid carcinomas and in 2 of the 3 malignant lymphomas. Of the 4 histologically verified epidermoid carcinomas of the series, 3 gave on oesophageal lavage a finding cytologically indicative of malignancy, while the gastric lavage performed on the fourth patient was a technical failure.

The cancer tissue of 22 histologically verified neoplasms of the series was highly anaplastic. On cytologic examination 13 specimens were considered to give a malignant and 6 a suspicious finding, while in 3 cases the finding was negative.

The site of the neoplasm. The most common site for a gastric carcinoma is the distal part of the stomach. This opinion was held even in the 19th century, for Brinton 18?? for example reported that gastric carcinoma affected the pyloric region in 60 per cent of cases while 10 per cent were situated in the cardia. This is doubtless true for approximately one-half of all gastric cancers occur in the pyloric canal or in the adjacent antrum. They are often the most malignant, with metastasis occurring frequently before the growth has achieved any remarkable size. Most tumours in the pars pylorica apparently begin on the lesser curvature of the antrum, eventually involving the pyloric canal. Excluding the pyloric region approximately 20 per cent of gastric cancers occur on or near the lesser curvature, about 7 per cent on or near the greater curvature and approximately 9 per cent in the cardia of the stomach. The remainder occur on the anterior and posterior wall of the body of the stomach (Bockus 1949).

The correlation of the cytologic finding *to the site of the neoplasm is a subject* that has already been studied. It has been claimed, for example, that the cytologic examination of prepylorically situated tumours often fails because of the complications of stenosis and gastric retention (e.g. Ulfelder et al. 1948, Swarts et al. 1950, Traut et al. 1952, Cooper and Papanicolaou 1953, ?abe et al. 1954, Umiker et al. 1958), but less attention has been paid to the cytologic finding for neoplasms elsewhere in the stomach. Carcinomas of the cardia of the stomach can obviously be relatively easily detected by cytologic means. Andersen and his co-workers (1949) in a series containing only oesophageal and cardial carcinomas cytologically detected 39 (92 per cent) out of 42 carcinomas of the cardia, and Umiker et al. (1958) obtained a cytologic finding indicating malignancy in 9 out of 12 cases. In their total series of 49 cancers of the stomach, a cytologic finding indicative of malignancy was obtained in 64 per cent (11 cases) of the neoplasms of the body and in all 3 cancers which involved a large portion of the stomach.

Neoplasms situated in the cardia or the fornix of the stomach are often difficult to detect by either x-ray or endoscopic examination, while neoplasms in the antrum may escape gastroscopic detection because of retention, poor visibility or some other reason. The cytologic results are therefore now compared with those obtained by x-ray or endoscopic examination. The neoplasms have been classified according to site. The series comprised

biopsy specimens, a study was undertaken to see whether the mean size of these cells was of significance in the fluctuation of mitotic frequencies. The cases were classified according to nuclear dimension the group with a mean nuclear dimension below 9 μ contained 18 cases with a mean mitotic frequency of 16.7 pro mille, and the group with a mean nuclear dimension of 9 μ or more contained 17 cases with a mean mitotic frequency of 19.1 pro mille. It was therefore concluded that nuclear size does not significantly affect mitotic frequency.

The mitotic frequencies were calculated for the biopsy material which had been classified malignant, suspicious or negative according to the cytologic finding. The mean mitotic frequency for the biopsy specimens of the group cytologically interpreted as malignant was 17.6 pro mille, in those considered suspicious 17.5 pro mille and in those classified as negative 17.2 pro mille. It was therefore concluded that there were no differences between the mitotic frequencies for biopsy specimens classified according to cytological finding.

Mitotic frequency in cytologic smears. Mitoses are not usually seen in cytologic smears taken in non malignant gastric diseases. None of the 627 specimens of the *non-malignant group* of the present series showed any normal or pathologic mitoses. In order to check this observation, a total of 3 000 cells in the cytologic smears of 15 patients were studied again either in clusters or singly for possible mitoses, but none was found. The majority of cells were from the gastric surface epithelium but gland cells were also present. Neither histiocytes nor other single cells showed mitoses.

The cytologic specimens of the 83 histologically verified gastric neoplasms of the *malignant group* were also examined for possible mitoses. In all 83 cases the cytologic study had given either a malignant or a suspicious finding. The mitotic figure was calculated for each case, either per 100 suspicious cells or if there were fewer cells, for all the suspicious cells found in the specimen.

Mitoses were found in 44 of the 83 cases (81 cases of gastric carcinoma and 2 cases of malignant lymphoma). There were many mitotic figures in single cells (Figs. 19 and 20) but most of them occurred in clusters. Table 17 shows the distribution of mitoses according to the histologically different types of neoplasm. When these results were treated statistically the occurrence of mitoses was not found to be related to the histological type of neoplasm. The mean mitotic frequency was 6.4 pro mille for the total



Fig. 19

A single mitotic figure in the cytological specimen of scirrhous carcinoma patient. Case 63/58.

cative of malignancy in 91.5 per cent of the cases while the percentage for gastroscopy was 86 and for x-ray examination 78. For neoplasms of the antral area, x ray examination gave a finding indicative of malignancy in 91.5 cytologic study in 79 and gastroscopy in 62 per cent of the cases, and understandably x ray examination also proved to be the best for widespread neoplasms. It gave a finding indicative of malignancy in each of the 16 cases of this group, while cytologic study produced a positive finding in 11 cases and gastroscopy in 6. In this group, too the gastroscopic results were impaired by the large number of unsuccessful examinations (8 out of 16

From all this it is clear that the diagnostic reliability of the methods of examination varies according to the site of the neoplasm in the different parts of the stomach In illustration Fig 16 presents a diagram of the results obtained by each of the three methods of examination, with the neoplasms classified according to site. The columns in the various parts of a schematically drawn stomach indicate the proportionate results for the relevant part by each method of examination, the length of the column indicates the number of cases.

Comment. In the present series, the histologic type of the neoplasm did not seem to affect the result of the cytologic examination to the extent that might perhaps have been expected from some earlier investigations. Raskin et al. (1960 it is true succeeded in detecting by gastric cytology 93 per cent of the neoplasms of their series, an indication that the histologic structure of the neoplasms, with the possible exception of linitis plastica, does not appreciably affect the successful performance of cytologic examination. In anaplastic carcinomas, the discovery of mitoses in the smears may confirm a finding which would otherwise remain cytologically inconclusive for in the present series at least mitoses were found relatively frequently in the cytologic smears from anaplastic carcinomas. The site of the neoplasm was not found to affect the success of the examination methods employed (gastric roentgen, cytology and gastroscopy) except that in widespread carcinomas and in those localized in the cardia, gastroscopy frequently failed. For neoplasms in the antrum, x-ray examination is obviously the most reliable method but for carcinomas situated elsewhere cyto-

...examinations in 118 gastric neoplasms classified according to site

Gastroscopy					Cytology				
malignant	suspicious	inconclusive	negative	technical failures	malignant	suspicious	inconclusive	negative	technical failures
2	—	1	2	8	6	3	—	2	2
23	8	2	1	2	22	11	2	1	—
14	15	8	3	7	15	22	3	4	3
6	—	1	1	8	7	4	2	2	1
	2	—	2	2	3	2	—	1	—
45 (38%	23 (21)	12 (10%)	9 (8%)	27 (23%)	53 (45)	42(35.5%)	7 (6%)	10 (8.5%)	6 (5)

Table 18 The mitotic frequencies found in the 81 cytologically malignant or suspicious specimens, classified according to the histologic type of neoplasm or to the number of suspicious cells found in the specimens.

Type of neoplasm	Number of atypical cells found in the cytologic specimens							Total		
	under 20	20-49	50-99	100-199	200-499	500-999	not less than 1000	Cases	Mitoses/cells	Mitotic frequency pro mille
Adenocarcinoma										
cases	5	3	9	12	11	2	2	44		
mitoses/cells	0/53	0/74	1/603	8/1632	23/3440	3/1136	16/2186		51/9144	5.6
Scirrhous carcinoma										
cases	—	4	2	1	2	—	—	9		
mitoses/cells	—	2/147	2/120	2/169	1/666	—	—		7/1102	6.4
Medullary carcinoma										
cases	1	2	3	—	1	2	2	11		
mitoses/cells	0/3	1/65	4/189	—	1/308	7/1192	13/2000		26/3757	6.9
Solid carcinoma										
cases	1	2	1	2	7	—	—	13		
mitoses/cells	0/18	0/67	1/50	1/275	21/2327	—	—		23/2737	8.4
Mucoid carcinoma										
cases	1	1	1	—	1	—	—	4		
mitoses/cells	0/4	0/20	0/58	—	3/245	—	—		3/327	9.2
Total										
cases	8	12	16	15	22	4	4	81		
mitoses/cells	0/78	3/373	8/1120	11/2096	49/6986	10/2328	29/4186		110/17067	
mitotic frequency pro mille		8.0	7.8	5.2	7.0	4.3	6.9			6.4

nomas than in other carcinomas, or the mitotic frequency is in fact higher

Comment. As can be seen from the foregoing, the incidence of mitoses in gastric cytology specimens is not so uncommon as was previously believed. Since mitoses were not found in the cytologic specimens from non-malignant gastric diseases, the presence of mitoses must undoubtedly be considered highly suggestive of malignancy It seems, therefore, that the presence of mitoses in gastric cytology specimens can be employed as an important criterion for malignancy the use of which may prove helpful in the cytologic diagnosis of anaplastic gastric carcinoma.

8. The diagnostic significance of nuclear size and mitotic division

In order to throw light on the practical importance of these two criteria of malignancy nuclear size and mitotic frequency part of the series was re-examined. All the specimens of the *malignant group* together with the false findings and

size of normal gastric cell and cells of gastric neoplasms in unstained gastric lavage specimens According to the results he published the nuclear sizes for the columnar epithelial and chief cells of the stomach were smaller than those for cells from gastric neoplasms or f om epidermoid carcinomas, but no conclusions could be drawn f om the observations he made Later Massey and Rubin 1954 measured the nuclea sizes of the P A cells" noted in the cytologi pecimens of patients with pernicious anaemia and found that they were defin tely larger than the nuclei of ord nary urface epithelium. Several authors, among them Schad (1958) have found that the size of lls n carcinomas varies considerably and that giant cells are not unusual but actual measurements ha apparently not been taken Raskin et al. (1958 claimed that many cancer cells are two or mor times the size of normal columnar cells and that the nucleus is so disproportionately increased n size that t may constitute as much as 80 per cent or mor of the cell S nce the size of the whole cell is often difficult to determine n gastric cytology smears, attention is focused n the following account on the measuring of the nucle size alone and on the diagnostic significance of this measurement of gastric cytology specimens.

A pecial effort was made to establish the size of nuclei that significantly indicated malignancy

Material and methods. Cytologic pecimens rarely contain cells exfoliated from the normal epithelium, and specimens obtained during operation or by suction biopsy were used to assist this investigation. Biopsy specimens were treated w th formalin fixation and haematoxyl in-eosin staining The sections were 4 μ thick. Nuclei were measured by means of an ocular micrometer the mean diameter of each nucleus being calculated from ts maximum diameter and the one at right angles to t. The mean diameter thus obtained will hereafter be referred to as the dimension The d mension of all intact and regula nuclei was found systematically for 100 nuclei n each case F om the cytologic smears the nuclei of gastric cells and P A cells and n cases of neoplasm, those of the atypical or suspicious cells vere measured It was no t alw ays possible to find 100 cells in t cytologic specimens from neoplasms, and measurements were therefore taken provided the smears show ed a minimum of 50 mal gnant or atypical cells.

The nuclea measurements are given n Table II The dimensions of the nuclei from ells of the gastric surface epithe l um and of glandular cells were deter mined in 6 histologically normal cases from specimens taken by suction biopsy from the body region. The dimensions of nuclei of the surface epithelium and of the glandular cells in the pylori region were obtained from 8 apparently normal b opsies taken on operation. Suction biopsy specimens were used to provide the dimensions of nuclei of the surface epithelium or of metaplastic changes in 13 cases of atrophic gastritis (including 6 cases of pernicious anaemia) and also in 6 cases of pseudopyloric glands. Nuclear dimensions for the surface epithelium and the metaplastic changes of 6 gastric ulcer patients were determined from biopsy specimens taken on operation. From these histologically studied cases,

Table 18. The mitotic frequencies found in the 81 cytologically malignant or suspicious specimens, classified according to the histologic type of neoplasm or to the number of suspicious cells found in the specimens.

Type of neoplasm	Number of atypical cells found in the cytologic specimens							Total		
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cases	—	4	2	1	2	—	—	9		
mitoses/cells	—	2/147	2/120	2/169	1/666	—	—		7/1102	6.4
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cases	1	2	3	—	1	2	2	11		
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Solid carcinoma										
cases	1	2	1	2	7	—	—	13		
mitoses/cells	0/18	0/67	1/50	1/275	21/2327	—	—		23/2737	8.4
Mucoid carcinoma										
cases	1	1	1	—	1	—	—	4		
mitoses/cells	0/4	0/20	0/58	—	3/245	—	—		3/327	9.2
Total										
cases	8	12	16	15	22	4	4	81		
mitoses/cells	0/78	3/373	8/1120	11/2096	49/6966	10/2328	29/4186		110/17067	
mitotic frequency pro mille		8.0	7.8	5.2	7.0	4.3	6.9			6.4

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Comment. As can be seen from the foregoing, the incidence of mitoses in gastric cytology specimens is not so uncommon as was previously believed. Since mitoses were not found in the cytologic specimens from non-malignant gastric diseases, the presence of mitoses must undoubtedly be considered highly suggestive of malignancy. It seems, therefore, that the presence of mitoses in gastric cytology specimens can be employed as an important criterion for malignancy, the use of which may prove helpful in the cytologic diagnosis of anaplastic gastric carcinoma.

8. The diagnostic significance of nuclear size and mitotic division

In order to throw light on the practical importance of these two criteria of malignancy, nuclear size and mitotic frequency, part of the series was re-examined. All the specimens of the *malignant group* together with the false findings and

Results. The cytologic and biopsy specimens were fixed and stained by various methods. In order to detect possible errors the nuclear sizes of specimens prepared by the cytologic and the biopsy methods were compared by taking adjacent specimens from surface epithelium cells of three different sites in one and the same patient and by fixing and staining them by both the cytological and the biopsy methods. The nuclear dimension of surface epithelium cells was then calculated for them. The results are given in Table 12. It was *found that the difference between the*

Table 12. The effect of cytologic and histologic fixation and staining techniques on the size of the nuclei of gastric surface epithelium cells in the measurements of three specimens from one patient.

Specimen	Mean nuclear dimension	Variance	Total of nuclei measured
No. 1 cytological	7.0	0.5	101
histological	7.1	0.4	100
No. 2 cytological	7.0	0.8	115
histological	6.9	0.8	100
No. 3 cytological	7.0	0.9	119
histological	7.1	0.6	101

mean nuclear dimensions obtained was not statistically significant, and it seems that each method changes the nuclei in the same way. Histologic preparations could therefore be in themselves useful for nuclear measurement and not merely provide a control for results.

Table 13 gives the mean nuclear dimensions and the variances for surface and glandular epithelia from patients with non-malignant gastric complaints. The measurements show that the mean dimension of all nuclei of glandular cells was under 6 μ, whereas larger nuclei were visible in the surface epithelium. The biggest nuclei measured for non-malignant cases were in specimens from patients with pernicious anaemia or gastric ulcer. In these specimens, the nuclei were mostly situated at the bottom of the tubuli, and their mean dimension varied from 6 to 7.9 μ (range 3—10 μ).

No cells reminiscent of "P. A. cells" were found in the biopsy specimens, but the nuclear dimension for a total of 303 P. A. cells in cytologic smears was *measured in 8 cases. The mean dimension* was 9.0 μ (standard deviation 1.3 μ; range 6—13 μ).

The nuclear dimension for cancer cells was measured from the biopsy specimens of 37 patients with gastric neoplasm. In 19 of these 37 cases, the nuclear dimension of cells of malignant appearance was also measured from cytologic smears. The results obtained in measurement of the nuclei in individual cases of neoplasm are given in Appendix 3. A comparison of measurement results shows that the mean nuclear dimensions obtained from biopsy specimens differed in some individual cases, from those obtained from cytological specimens. This was probably the result of a variation in nuclear size within the neoplasm, since similar differences were found on control measurement within one biopsy specimen. On the other hand, the mean of the nuclear dimensions calculated from the biopsy specimens of the whole series is virtually the same as that of the nuclear dimensions measured from the cytologic specimens. This can be seen from Table 14, which compares the measurements obtained

SUMMARY

A cytologic examination of the stomach was performed by the chymotrypsin method (or Ringer lavage) on 736 patients, 151 of whom had a malignant neoplasm in the stomach or the distal part of the oesophagus. The diagnosis of a neoplasm had been verified bioptically or operatively in 117 cases. In the rest of the cases diagnosis was verified by subsequent follow-up examination.

Cytologic examination gave a finding indicative of malignancy (i.e. malignant or suspicious) in 80.5 per cent of the cases of neoplasm, and a finding falsely suggestive of malignancy in 2 per cent. The diagnostic reliability of cytologic examination was compared with that of x ray examination and gastroscopy. Gastric x-ray revealed 82 per cent and gastroscopy 59 per cent of the gastric neoplasms, but the gastroscopy results were adversely affected by unsuccessful examination. The use of all three examination methods increased diagnostic reliability to such an extent that of the 118 cases, there were only 2 in which none of the three examination methods gave any finding indicative of malignancy.

Neoplasms of the gastric body were best detected by cytology or gastroscopy but those located elsewhere in the stomach were most reliably detected by x ray examination. The histologic structure of the neoplasm was not found to have any distinct effect on the success or failure of the cytologic examination.

The mean of average diameters of the nuclei of gastric cells measured in biopsy specimens from the *non-malignant group* was biggest in pernicious anaemia and gastric ulcer cases. The figure for their metaplastic changes and surface epithelium was 7.0 μ (standard deviation 1.1 μ). In the cytologic specimens, the mean dimension of P. A. cells was 9.0 μ (standard deviation 1.3 μ). The mean dimension of malignant cells was 8.9 μ in the biopsy and 9.0 μ in the cytologic, specimens (standard deviations 1.9 μ and 1.8 μ, respectively).

Employing statistical probability it was calculated from the normal distribution that where the nuclear size of an otherwise atypical cell exceeded 13 μ the finding indicated gastric cancer with statistically significant probability (provided the cells were not P. A. cells). The reliability of the finding, however depended on the number of atypical cells present.

The mean mitotic frequency in cancer tissue, calculated from the biopsy specimens of the series, was 17.5 pro mille (standard deviation 8.1) in the cytologic

Table 14. A comparison of the distribution of nuclear dimensions of cancer cells in biopsy specimens (57 cases) and cytologic specimens (17 cases) from 57 gastric neoplasms.

Nuclear dimension μ	Biopsy specimens		Cytologic specimens	
	Number of cells	pro mille	Number of cells	pro mille
4	3	6	1	1
5	43	1	4	2
6	237	63	69	44
	566	151	233	148
8	852	227	412	261
9	48	700	291	184
10	689	184	304	194
11	246	66	106	67
12	184	49	79	50
13	83	22	39	23
14	41	1	23	15
15	11	3	10	6
1	4	1	3	
1		2	1	1
18	1	1	1	
19	1			—
20	2	1		
21	1			
Total	3 48	1 000	1 578	1 000

from biopsy and cytologic specimens. The mean nuclear dimension for cancer cells in the biopsy specimens was 8.9 μ standard deviation 1.9 μ; the mean nuclear dimension for suspicious cells in the cytologic specimens was 9.0 μ standard deviation 1.8 μ. The range of nuclear dimensions in the biopsy specimens was 4–21 μ and in the cytologic specimens, 4–18 μ. In other cases not tabulated here cytologic specimens showed nuclei which even exceeded 20 μ in size. As an example of the cells with giant nuclei found in the cytologic specimens, Fig. 17 shows a cell with a giant nucleus measuring 18 μ and Fig. 18 one measuring 22 μ.

Nuclear size was not found to be related to the histologic type of the



Fig. 17
Giant nuclear cell, the nuclear dimension was 18 μ. Biopsical: mucoid carcinoma. Case 168/58

LITERATURE

ANDERSEN, H. A., MCDONALD, J. R. AND OLSEN, A. M.: Cytologic diagnosis of malignant lesions of the esophagus and cardia of the stomach. Minn.Med. 32:1181–1185:1949.

AYABE, M., OTA, T., AND IZAKI, S.: Studies on cytological diagnosis of the gastric cancer. Yonago Acta med. 1:55–63:1954.

AYRE, J. E., AND OREN, B. G.: New rapid method for stomach-cancer diagnosis: The gastric brush. Cancer 6:1177–1181 1953.

BACH-NIELSEN, P. AND AND UP E.: Cancerceller i entriheltsinllevand. Chymotrypsinmetoden. Ugeskr. Laeg. 122:40–43 1960

BENEDICT, E. B.: Endoscopy. New Engl. J. Med. 241:152–154:1949

BERKSON, J., WALTERS, W., GRAY, H. K., AND PRIESTLEY, J. T.: Mortality and survival in cancer of the stomach: A statistical summary of the experience of the Mayo Clinic. Proc.Mayo Clin. 27:137–151 1952.

BLOMQUIST, H. E.: Mahasyövän talda suonteton reaktion myohälstuloiset. Duodecim 72:472–475:1956.

BOAS, I.: Diagnostik und Therapie der Magenkrankheiten. I. Teil. 4. Aufl. Georg Thieme Leipzig 1897

BOCKUS, H. L.: Gastro-Enterology. Vol. I. The esophagus and stomach. W. B. Saunders, Philadelphia 1949

BOLKER, N.: Early diagnosis of carcinoma of the stomach. Ann.intern.Med. 30:903–915:1949.

BOTSFORD, T. W. AND TUCKER, M. R.: Application of cytologic smear methods to cancer diagnosis in general hospital. J.A.M.A. 142:975–979:1950.

BRENNER, A. J., KORNSTEIN, A., BANDLER, M., MATZNER, M. J.: Present status of gastric cytology. A study of 60 cases by the chymotrypsin method. Amer. J Gastroent. 30:415:1958.

BRINTON, W.: Die Krankheiten des Magens. Druck und Verlag der Stahel'schen Buch- und Kunsthandlung, Würzburg 186..

BROWNE, D. C., MITCHELL, R., WELCH, G. AND SORRELL, W.: Evaluation of gastric exfoliative cytology. Gastroenterology 28:964–968:1955.

BRYANT, H. C., CRAIG, W. R., AND POLLARD, H. M.: Cytologic study of gastric aspirate for carcinoma cells. J.nat.Cancer Inst. 10:459–466: 1949

BURNETT, W., MACFARLANE, P.S., SCOTT PARK, S.D., AND KAY, A.W.: Carcinoma of the stomach. Brit. med. J. I:753–755:1960.

CABRE FIOL, V.: Procedimiento de obtención de muestras para citologia endogástrica. Rev.esp. Enferm.Apar.dig. 12:186–189:1953.

CARDOZO, P. L.: Clinical cytology using the May-Grünwald-Giemsa stained smear. I–II. L.Stafleu, Leyden 1954.

CHAPMAN, D. L. S., KLOPP, C. T. AND PLATT, L. I.: Application of balloon technique in detection of cancer. Cancer 6:1174–1176:1953

COMAN, D. R.: Decreased mutual adhesiveness, property of cells from squamous cell carcinomas. Cancer Res. 4:625–629:1944

COMMITTEE ON NOMENCLATURE OF TUMORS: Histological nomenclature of human tumors. Acta Un.Int.Cancr. 14:149–233.1958.

CONTE, M., AND CONTE MARTI, MME: Cytodiagnostic du cancer gastrique. Gastroenterologia 85:257–270:1956.

COOPER, W. A., AND PAPANICOLAOU, G. N.: Balloon technique in the cytological diagnosis of gastric cancer. J.A.M.A. 151:10–14:1953.

DABNER, A., ETCHEVERRY, R., KATZ, R., AN GUZMAN, C.: Investigacion de celulas neoplasicas en el contenido gastrico y material obtenido con balon insuflable de Panico-Papanicolaou. Rev méd. Chile 79:766–768:1951

DOLL, R.: Environmental factors in aetiology of cancer of the stomach. Gastroenterologia 86:320–328:1956.

EWALD, C. A.: Klinik der Verdauungskrankheiten, II. August Hirschwald, Berlin 1893.

FISCHMAN, M., AND TERRANO, G.: Citología gastrica, metodo del balon abrasivo de Panico, Papanicolaou y Cooper. Acta Un.Int.Cancr. 14:923–932:1958.

F Y O A., PRIESTLEY, J. T., COMFORT, M. W. AND GAGE, R. P.: Total Gastrectomy: Mortality and Survival. Ann. Surg. 147:760–768:1958.

FREMONT SMITH, M., GRAHAM, R. M., AND MEIGS, J. V.: Early diagnosis of cancer by study of exfoliated cells. J.A.M. 469–474 1948.

ELSNER, H.: Frühdiagnose des Magenkarzinoms. Berl.Klinik 20:1–22.1908.

of which the last two are conditional. The estimate obtained for the probability $P(m > r_2)$ is

$$P(m > r_2) = P(m > r \quad m(\bar{x}_r) < r_1) \; P(m(\bar{x}) < r) + P(m \quad r \quad m(x) > r) \; P(m(x_r) > r_1) < \epsilon_3 + \epsilon_1$$

That obtained for probability $P(x^* > \quad)$ which determines the final probability level, is

$$P(x^* > r_4) = P(x^* > \quad m_r \; \sigma < \} r_2) \; P(m < r) P(\sigma < \} r_2) + P(x^* > r \quad m_r > r \; \sigma < \} r_2) \; P(m > \quad) P(\sigma < \} r) + P(x^* > \quad m_r < \; \sigma > \} \;) \; P(m \quad r) P(\sigma > \}' \;) + P(x^* > \quad m_r > \; \sigma > \} r) \; P(m \quad r) P(\sigma > \} r_2) < \epsilon + \epsilon + \epsilon_3 + \epsilon_2 + (\epsilon + \epsilon_3) \epsilon_2 = \epsilon$$

It was subsequently found that for every patient the nuclear dimension of a cell *other than a cancer or P. A. cell*, with a reliability higher than

$$1 - \quad = 1 - \left[\Sigma \quad + \epsilon \; (\epsilon + \epsilon) \right]$$

is smaller than

A study was now made of n cells suspected to be cancer cells on the basis of criteria other than the nuclear dimension. If the nuclei of k cells have a dimension not less than r_4 cancer is a possibility with a reliability exceeding $(1-\epsilon)$

$$\epsilon = \binom{n}{k} \epsilon_3^k \; (1-\epsilon_3) \quad ^k$$

From the combined pernicious anaemia and gastric ulcer series two alternatives were determined for ϵ_4 and r_4 with the values

$x = 6.98 \qquad \sigma(x) = 0.60$

$= 0.90 \qquad \sigma(x^2) = 0.27$

The results were:

A	0.0005	0.0005	0.0005	0.001	0.0025
	7.55	1.16	9.53	12.87	
B	0.00003	0.00005	0.00005	0.00015	0.0003
	7.65	1.20	9.99	13.94	

The former suggests that for every patient the nuclear dimension of every non-malignant cell is less than 15 μ with a probability that is at least statistically significant ($\epsilon = 0.0025$). The latter suggests that the limit 14 μ gives a minimum of highly significant probability ($\epsilon = 0.0003$).

Since in practice there are usually more cells *suspicious for malignancy*, Table 15 shows the fluctuations in statistical significance according to the number of cells found accompanying such a giant nucleus. The presence of a nucleus 15 μ in size among 5 cells remains statistically at least significant ($\epsilon = 0.01$) and the presence of a cell this size among 20 suspicious cells would be statistically at least almost significant ($\epsilon = 0.05$).

Nieburgs, H. E.: Cytologic technics for office and clinic. Grune & Stratton, New York 1956.
Nieburgs, H. F., Wertheim, J. L., Hollander, F., and Janowitz, H. D.: Cytologic diagnosis of gastric cancer and evaluation of the abrasive brush technic in 125 cases. Amer. J. dig. Dis. 5:63—72:1960.
Pack, G. T.: Diagnosis of cancer of the stomach. N. Y. St. J. Med. 53:390—392:1953.
Panico, F. G.: Cytologic criteria of gastric cancer. Surg. Gynec. Obstet. 97 II:233—243:1953.
Panico, F. G., Papanicolaou, G. N., and Cooper, W. A.: Abrasive balloon for the exfoliation of gastric cancer cells. J. A. M. A. 143:1308—1311: 1950.
Papanicolaou, G. N.: Atlas of exfoliative cytology. Harvard University Press, Cambridge, Mass. 1954.
Papanicolaou, G. N., and Cooper, W. A.: Cytology of the gastric fluid in the diagnosis of carcinoma of the stomach. J. nat. Cancer Inst. 7:357—360:1947.
Papanicolaou, G. N., and Traut, H. F.: Diagnosis of uterine cancer by the vaginal smear. The Commonwealth Fund, New York 1943.
Pollard, H. M., Bryant, H. C., Block, M., and Hall, W. C.: Diagnosis of gastric neoplasms by cytologic examination of gastric secretions. J. A. M. A. 139:71—74:1949.
Pollard, H. M., and Cooper, R. R.: Hypertrophic gastritis simulating gastric carcinoma. Gastroenterology 4:453—465:1945.
Ransom, H. K.: Cancer of the stomach. Surg. Gynec. Obstet. 96:275—287:1953.
Raskin, H. F., Kirsner, J. B., and Palmer, W. L.: Exfoliative cytology of the gastro-intestinal tract. Modern trends in gastro-enterology (Second series). Ed. by F. A. Jones. Butterworth & Co, London 1958. Pp. 76—91.
Raskin, H. F., Kirsner, J. B., Palmer, W. L., Pleticka, S., and Yarema, W. A.: Gastrointestinal cancer definitive diagnosis by exfoliative cytology. Arch. Surg. 76:507—516:1958.
Raskin, H. F., and Pleticka, S.: Exfoliative cytology of the stomach. CA (N. Y.) 10:82—89: 1960.
Rehfisch: Diagnose des Magencarcinoms aus Spülwasser und Erbrochenem. Dtsch. Arch. klin. Med. 58:62—70:1897.
Riess, L. D., Rider, J. A., and Frost, J. K.: Exfoliative gastric cytology. Amer. J. med. Sci. 231:249—252:1956.
Richardson, H. L., Queen, F. B., and Bishop, F. H.: Cytohistologic diagnosis of material aspirated from stomach, accuracy of diagnosis of cancer, ulcer and gastritis from paraffin-embedded washings. Amer. J. clin. Path. 19: 328—340:1949.
Rechem, Cl., and Lambli…, A.: Analyse critique du cyto-diagnostic gastrique. A l'occasion de 163 cas personels. Arch. Mal. Appar. dig. 47: 1153—1162:1958.
Rohrbach, O.: Über die Anwesenheit von Geschwulstpartikeln in dem durch die Magenpumpe entleerten Mageninhalte bei Carcinoma ventriculi. Dtsch. med. Wschr. 8:452—453:1882.
Rosenheim, Th.: Pathologie und Therapie der Krankheiten des Verdauungsapparates mit besonderer Berücksichtigung der Diätetik. I. Theil. 2. Aufl. Urban & Schwarzenberg, Wien 1896.
Rosenthal, M., and Traut, H. F.: Mucolytic action of papain for cell concentration in the diagnosis of gastric cancer. Cancer 4:147—149: 1951.
Ross, J. R., McGrath, J. M., Crozier, R. E., Rohart, R. R., and Middleton, M.: Exfoliative cytology: its practical application in the diagnosis of gastric neoplasms. Gastroenterology 34:24—33:1958.
Rossman, M., and Wolf, J.: Accidental gastric biopsies with the Ayre brush. Gastroenterology 30:686—689:1956.
Rubin, C. E., and Benditt, E. P.: Simplified technique using chymotrypsin lavage for the cytological diagnosis of gastric cancer. Cancer 8:1137—1141:1955.
Rubin, C. E., and Massey, B. W.: Preoperative diagnosis of gastric and duodenal malignant lymphoma by exfoliative cytology. Cancer 7:271—288:1954.
Rubin, C. E., Massey, B. W., Kirsner, J. B., Palmer, W. L., and Stonecypher, D. D.: Clinical value of gastrointestinal cytologic diagnosis. Gastroenterology 25:119—138:1953.
Ruiz Martinez, A.: Technik zur Entnahme von Zellen aus dem Speiseröhre — Magenabschnitt mittels einer neuen Methode der Zellabschürfung und Ausspülung. Internationales Symposion über klinische Cytodiagnostik. Hrsg. von N. Henning und S. Witte, Georg Thieme Verlag, Stuttgart 1958.
Ruuskanen, J. W.: Redogörelse över två fall af ventrikelkarcinom. Utdrag ur protokollen förda vid Finska Läkaresällskapets sammanträde den 11 november 1893. Finska Läk.-Sällsk. Handl. 35:936:1893.
Sahli, H.: Lehrbuch der klinischen Untersuchungs-Methoden. I Band. 6. Aufl. F. Deuticke, Leipzig 1913.
St. John, F.B., Sandweiss, P.C., and Harvey, H.D.: Experiment in early diagnosis of gastric carcinoma. Ann.Surg. 119:225—231:1944.
Saltzman, F.: Studien über Magenkrebs mit besonderer Berücksichtigung der Veränderungen in der Magenschleimhaut und der im Tumor und an dessen Rand auftreten den Rundzelleninfiltration. Arb. path. Inst. Univ. Helsinki. I. Band. Fischer, Jena 1913. Pp. 335—440.
Saxén, E.: Report from the Finnish cancer registry. Schweiz. Z. allg. Path. 18:556—562:1955.
Saxén, E., and Korpela, A.: Uusien syöpätapausten esiintyminen Suomessa 1954. Suom. Lääk. L. 13:741—769:1958.

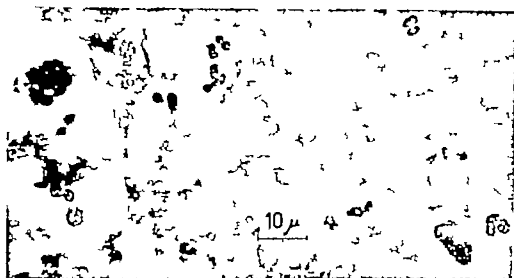


Fig. 20.

A single mitosis and giant nuclear cell in the cytological specimen of solid carcinoma patient. Case 14/59.

Table 17 The incidence of mitoses in 43 cytologically malignant or suspicious specimens obtained by chymotrypsin lavage, classified according to the histologic type of the gastric neoplasm.

Type of neopl n	Mitoses found	Mitoses not found
Adenocarcinoma	20 cases	24 cases
Scirrhous carcinoma	5	4
Medullary	8	3
Solid	8	5
Mucoid	1	3
Malignant lymphoma	2	—

series examined. Table 18 gives in detail the mitotic frequencies noted in the 81 gastric carcinoma cytologic specimens classified by histologic type of neoplasm and by number of suspicious cells found in the specimens. There was no statisti cally significant difference between th mitotic frequencies for histologically different types of neoplasm nor in the average size of nuclei in th specimens. The comparable difference was greatest between the frequencies for solid carcinoma and adenocarcinoma but it was not statistically significant.

The structure of the neoplasm was studied in 19 biopsy specimens of histologically different types of neoplasm that were highly anaplastic. The mean mitotic frequency for these anaplastic neoplasms was 7 8 pro mille, while for the remaining cases it was 5 9 pro mille. The difference in mitotic frequency between these groups, therefore was not statistically significant. Of the 19 anaplastic cases, the cytologic smears of 14 showed at least one mitosis, but only 25 of the 62 non-anaplastic cases showed mitosis, which is a significantly higher incidence ($\varepsilon = 0.01$) The inference is therefore that either there are more atypical cells in the cytologic smears of anaplastic carci-

APPENDIX 1

Table 20. Distribution by age of the 86 male and 56 female patients with gastric neoplasm compared with that of the 364 male and 221 female patients of the non-malignant series.

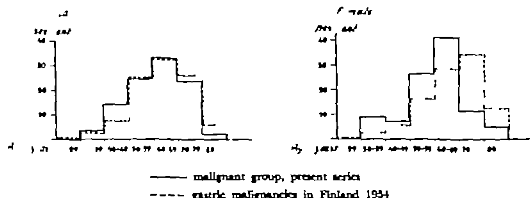
Male

Age group	Malignant		Non-malignant	
	Cases	Per cent	Cases	Per cent
under 29	–	–	9	2.5
30–39	3	3.5	35	9.5
40–49	12	14	104	28.5
50–59	21	24.5	108	30
60–69	28	32.5	79	21.5
70–79	20	23.5	25	7
over 80	2	2	4	1

Female

Age group	Malignant		Non-malignant	
	Cases	Per cent	Cases	Per cent
under 29	–	–	10	4.5
30–39	5	9	18	8
40–49	4	7	55	25
50–59	15	26.5	61	27.5
60–69	23	41	57	26
70–79	6	11.5	18	8
over 80	3	5	2	1

Fig. 21. Distribution by age of the 86 male and 56 female patients with gastric neoplasm compared with that of the proved gastric cancer cases diagnosed in Finland in 1954 (1151 men and 990 women, according to Saxén and Korpela)



the inconclusive specimens of the *non malignant group* were re-examined without identification under the microscope. The results are given in Table 19 where the results of the original cytologic examination and those of the microscopic re-examination are compared.

Suspicious cells were found in previously unexamined specimens of three *malignant group* cases which had formerly been considered cytologically as negative. None of the inconclusive cases of the *malignant group* showed mitoses or cells with giant nuclei. The criteria proved useful for the confirmation of suspicious findings the strength of them, an earlier previous finding was declared malignant 24 malignant group cases 17.5 per cent. No mitoses were observed in the false-suspicious and inconclusive cases of the *non-malignant group*. One case incorrectly interpreted as suspicious showed P. A. cells with a nuclear dimension exceeding 13 μ.

To sum up nuclear size and mitotic division, as criteria for malignancy may contribute towards increasing the reliability of gastric cytology findings, and more attention than hitherto might well be paid to their use.

Table 19. The results of the original cytologic examination and the microscopic re-examination of 721 specimens obtained by the chymotrypsin lavage method. In the re-examination, the measurement of nuclear size and the establishment of mitoses were used to help determine cytologic malignancy

	Cytologic finding				Technical failure
	malignant	suspicious	inconclusive	negative	
Malignant group 158 cases					
Original examination, per cent	47	34	6	9.5	3.5
Re-examination, per cent	64.5	19	6	7	3.5
Non-malignant group 563 cases					
Original examination, per cent	0.2	1.8	6	90	2
Re-examination, per cent	—	1.5	6.5	90	2

APPENDIX 3

Table 21 Nuclear dimensions of 3748 cancer cells from biopsy specimens (B) of 37 gastric neoplasms and 1578 cancer

Adenocarcinoma patients																												
Nuclear dimension	Cases																											
	1		2		3		4		5		6		7		8		9		10		11		12		13		20	21
μ	B	C	B	C	B	C	B	C	B	C	B	C	B	C	B	C	B	C	B	C	B	C	B	C	B	C	B	B
4		1																										
5	1	3	1										1					1										1
6	10	9	1	10	3	2	1		1		3	1	14	3	10	7		6	13	2			6	3		4	13	10
7	39	20	8	28	18	8		7	9	3	18	3	36	19	20	4		6	25	12	5		24	1	5	14	23	39
8	40	17	22	45	34	21	9	1	20	11	34	33	30	42	28	18	10	10	33	25	26	2	26	25	18	23	33	40
9	11	1	20	32	17	11	24	2	17	17	17	26	7	22	20	5	40	12	17	8	22	11	11	27	17	20	17	11
10	8	7	23	21	24	14	28	15	31	34	24	28	6	11	16	5	25	20	10	4	32	8	18	21	22	21	10	8
11			6	12	3	2	9	7	2	11	3	9	4		3		14	14	1	2	7	3	6	2	13	2	1	
12			11	5	4	2	15	3	8	15	4	3	2	1	2		8	8	2		7	10	4		5	7	2	
13	1	1	5			1	3	5	5	3	2	1		1				8			1	4	2			3		1
14				1			8	1	4					1				4	1			5				2	1	
15			1						1	3					2		1	3				3			1	1		
16							1		1									1										
17			1				1		1									1										
18							1			1														1				
19																												
20																												
21																												
Biopsy specimens																												
Nuclear mean dimension	9.2 μ																											
Mean variance	12.3																											

tions and in cytologically false-neg t or inconclusive cases, the poor quality of smears (as a result of retention or other factors) and in some instances the intramural location of the neoplasm the stomach interfered with the examination. In 3 cases malignant cells escaped detection because, accord ng to rul only 4 smears had been studied and cytologic changes ind cative of malignancy were only found later on microscopic re-examination of previously unexamined smears. Since changes suggestive of malignancy were in cases of neoplasm usually noted in the first cytologic smear it was not thought necessary to study all the smears after the first four had proved negative. It should be a matter of course that if the cytologic finding does not concur with the clinical finding, the unexamined smears should be studied prior to any re-examination.

From a comparison of the results obtained on cytologic study with the x ray findings, the diagnostic accuracy of the two methods seemed similar X ray examination gave a finding indicative of malignancy in 82 per cent and cytologic examination in 80.3 per cent of the cases of gastric neoplasm. Gastroscopy gave the finding less frequently (59 per cent) but this was due to the large number of unsuccessful examinations (23 per cent) in which the tube could not be passed through the cardia into the stomach.

In the present series, a distinct variation was noted in the reliability of the different methods of examination for detection of neoplasms in the various parts of th stomach. X ray examination was best for the detection of antral and widespread gastric neoplasms while those in the body

a ... gy d ... the cardia ... etec by ... s obtained in ... nation of the ... agreed both ... indicative of ... half the 13 cases of

... simultaneous use of the diff methods of examination is ... by the fact that the findings ... malignancy were in part complementary There were only two (1 3 per cent of the 118 patients examined by all three methods — gastric x ray gastroscopy and cytologic examination — f whom at the time of examination neoplasm was not suspected by any of the methods. In the present series, because of the criteria for examination the x ray finding suggested malignancy in every 6th case (16 4 per cent) of the *non-malignant group* Furthermore, since gastric x-ray was often unable to eliminate the possibility of malignancy the need for complementary diagnostic methods was obvious. On the strength of the experience gained cytologic examination as well as gastroscopy seems to be suited to complement gastric x-ray examination, and the simultaneous use of all three methods is undoubtedly useful.

The importance was assessed of the measurement of nuclear size and mitotic division in the cytologic specimens, for confirmation of a cytologic suspicion of malignancy It was verified that different methods for the fixation and staining of biopsy and cytologic specimens did not affect the nuclear size and that measurements obtained by the cytologic and

specimens, the mitotic frequency of cyto-
logically suspicious cells averaged 6 1 pro
mille In gastric cancer cases, a minimum
of one mitosis per case was noted
almost half the cytologically succe
specimens.

Mitoses were particularly evident i
cytologic specimens of anaplastic carci
nomas, although the mitotic frequency
obtained for such carcinomas in biopsy

FRIEDRICH, H. W. Über den Wert der ... gleichen Magensaftuntersuchung f... d... D... des Magencarcinoms. Arztl.Wschr. 6 ... 1951.

FRIEDMAN, R. L., AND GORDON, M. C. D... significance of the examination of ... ings in patients suspected of cancer ... Klin.Med. 70:59 – 67 191...

GARRET, M., RATH, H. ... PAR ... C... parison of the balloon and la... gastric cancer detection and illustra... cytological patterns of gastric cancer. C... 13:192 – 199 1960.

GIBBS, D. D.: Gastric Cytodiagnosis. A Re... and appraisal. Gut 1:203 – 216 1960.

GLADSTONE, S. A. Use of sponge in ... tissue from stomach for biopsy. Amer. J. ... Path. 19:891 – 894 1949.

GRAHAM, R. M. AND RHEAULT, M. H. Characteristic cellular changes in epithelial ce... pernicious anemia. J.Lab.clin.Med. ... 245 1954.

GRAHAM, R. M., ULFELDER, H., ... C... T. H. Cytologic method as an aid in the diagnosis of gastric carcinoma. Surg.Gynec.Obstet. 8... 237 – 239 1948.

GRA... D. R., ... WARD, G. E. Delay in diagnosis of carcinoma of the stomach. An analysis of 104 cases. Amer.J.Surg. 83:521 – 526 1952.

CHINEA, O. F., TR... H. F., WOOD, D. A., FARBER, S. H.: Clinical report on the cytologic diagnosis of gastric cancer. Surg.Gynec.Obstet. 98: 347 – 352 1954.

GUTMANN, L. W. End results for gastric cancer. 2891 cases. Surg.Gynec.Obstet., suppl. 93:313 – 331 1951.

GUTMANN, R. A.: Diagnostic précoce du cancer gastrique. Gastroenterologia 77:65 – 72 1951.

HECHT, E. L., ... COHEN, C.: Cytologic method in gastrointestinal cancer. Rev.Gastroent. 20: 11 – 20 1953.

HEMMETER, J. C.: Early diagnosis of cancer of the stomach. New York medical record 92:577 – 583 1899.

HENNING, N., ... WITTE, S.: Atlas der gastroenterologischen Cytodiagnostik. Georg Thieme Verlag, Stuttgart 1957.

HENNING, N. AND WITTE, S. Über eine neue Methode zur Zytodiagnostik der Magenkrankheiten. Dtsch.med.Wschr. 77:1 – 4 1952.

HITCHCOCK, C. R., MACLEAN, L. D., AND SULLIVAN, W. A. Secretory and clinical aspects of achlorhydria and gastric atrophy precursors of gastric cancer. J.nat.Cancer Inst. 18:795 – 811 1957.

HJEL... L.: Cytodiagnosis in pulmonary cancer. Ann.Chir.Gynaec.Fenn. 42: suppl. 3:1 – 68 1953.

JENKINSON, E. E., AND COLP, R.: Gastric carcinoma. A statistical study based on 344 cases from 1938 through 1947. Surg.Gynec.Obstet. 95:99 – 112 1952.

JENCHAL, E., Zytodiagnostik des Magenkrebses

... mit Hilfe ... mal ca... ... Lancet ... 1954

... Zytologie ... Diagnostik des ... Magencarcinoms ... 1934

LAW ... S. E. ... AND ... L. Cancer of the stomach. Amer. J. Surg. 81:2... – 226 1951.

LAURIN ... M. AND ... AND ... W. J. X-ray and gastroscopy findings in gastric cancer. 91 cases verified as gastric cancer ... follow-up. Ann. Med. Intern. Fenn. 49:27 – 32 1960.

LEMON, H. M. Application of cytologic diagnosis to cancers of the stomach, pancreas and biliary system. Ann. Intern. Med. 37:525 – 533 1952.

LOEPER, M. ... BINET, M. E. Cyto-diagnostic des affections de l'estomac. Bull. Soc. Méd. hôp. Paris 31:563 – 74 1911.

MCCUTCHEON, M., COMAN, D. R., ... MOORE, F. B. Studies on invasiveness of cancer. Cancer 1:460 – 467 1948.

MCNEER, G., LAWRENCE, W. JR., ASHLEY, M. P. AND PACK, G. T. End results in the treatment of gastric cancer. Surgery 43:879 – 896 1958.

MARTINSEN, J. M. A... MYTTING, I. Tumorceller i ventrikelsekret. Nord. Med 43:56 – 59 1950.

MARINI, G., Über die Diagnose des Magencarcinoms auf Grund der cytologischen Untersuchung des Spulwassers. Einige Beobachtungen über den normalen und pathologischen Zelleninhalt des Magens. Arch. Verdau. kr. 15:251 – 267 1909.

MASSEY, B. W. AND RUBIN, C. E. Stomach in pernicious anemia, cytologic study. Amer. J. med. Sci. 227:481 – 492 1954.

MEIGS, J. V., GRAHAM, R. M., FREMONT-SMITH, M., KAPNICK, I., AND RAWSON, R. W. Value of the vaginal smear in the diagnosis of uterine cancer. Surg. Gynec. Obstet. 77:449 – 461 1943.

MÜLLER, H.: Gezielte Entnahme von Material aus dem Magen für zytodiagnostische Zwecke mit Hilfe einer seitlich ansaugenden, flexiblen Probesonde. Z. ges. inn. Med. 8:779 – 781 1953.

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SCHADE, R. O. K.: Gastric cytology. Arnold, London 1960.
SCHADE, R. O. K.: Zytologische Diagnose des Magenkarzinoms. Verh. dtsch. Ges. Path. 39 Tagung gehalten in Zürich vom 1.–4. Juli 1955. Gustav Fisher Verlag, Stuttgart 1956. Pp. 292–294.
SCHINDLER, R.: Gastroscopy. The University of Chicago Press, Chicago 1950.
SEPPÄLÄ, K., LEHTINEN, M., KAIPAINEN, W. J.: Clinical importance of exfoliative gastric cytology. Ann. Med. intern. Fenn. 49:87–92: 1960.
SEYBOLT, J. F. AND PAPANICOLAOU, G. N.: Value of cytology in the diagnosis of gastric cancer. Gastroenterology 33:369–377:1957.
SEYBOLT, J. F., PAPANICOLAOU, G. N. AND COOPER, W. A.: Cytology in the diagnosis of gastric cancer. Cancer 4:286–295:1951.
SIGARD, A., GODET, R., MARSAN, C., AND THIELEN, R.: Valeur de la cytologie dans le diagnostic des affections gastriques. Presse méd. 64:537–539:1956.
SIURALA, M.: Gastric lesion in some megaloblastic anemias with special reference to the mucosal lesion in pernicious tapeworm anemia. Acta med.scand. suppl. 299:1–47 1954.
SIURALA, M., ERÄNKÖ, E., AND TAPIOVAARA, J.: Pernicious anemia and gastric carcinoma. Acta med. scand. 164:431–436 1959.
SIURALA, M., AND SEPPÄLÄ, K.: Atrophic gastritis as possible precursor of gastric carcinoma and pernicious anemia. Acta med.scand. 166: 455–474 1960.
STAFF OF THE VINCENT MEMORIAL HOSPITAL. Cytologic diagnosis of cancer. Saunders, Philadelphia 1950.
STATE, D., GAVSER, D., HUBBARD, T. B. AND WANGENSTEEN, O.H.: Early diagnosis of gastric cancer. J.A.M.A. 142:1128–1133:1950.
SWARTS, J. M., RAGINS, A. B., BERNSTEIN, A., AND MEYER, J.: Diagnosis of gastric cancer by cytologic examination of gastric washings. Gastroenterology 14:265–274 1950.
SWINNERTON, B. F. AND TUCKLOVE, B. G.: Carcinoma of the stomach. Brit. med. J. I:287–292:1955.
TANNER, N. C.: Critique of gastroscopy. Brit. med. J. II:819–831 1914.
TEMPLETON, F. E.: Errors in diagnosis of gastric carcinoma. Gastroenterology 28:378–387 1955.
TOMENIUS, J. H.: Cytological diagnosis of gastritis. Acta med. scand. 123:417–427 1946.
TOMENIUS, J. H.: Study on the gastric sediment. Acta med.scand. suppl. 183:1–198:1947.
TRAUT, H. F., ROSENTHAL, M., HARRISON, J. T., FARRER, S. M., AND GRIMES, O. F.: Evaluation of cytologic diagnosis of gastric cancer. Surg. Gynec. Obstet. 95:709–716:1952.
TUOMIKOSKI, V.: Mahasyövästä ja sen leikkaushoidosta. Duodecim 53:31–85:1937.
ULFELDER, H., GRAHAM, R. M., AND MEIGS, J. V.: Further studies on the cytologic method in the problem of gastric cancer. Ann. Surg. 128:422–424 1948.
UMIKER, W. O., BOL, R. J., HOEKSEMA, A. D., AND POLLARD, H. M.: Cytology in the diagnosis of gastric cancer. The significance of location and pathologic type. Gastroenterology 31:859–866:1958.
WALSHE, W. H.: Physical diagnosis of diseases of the lung. London 1843. Cited by L. Weiss, Brit. J. clin. Pract. 13:272–274 1959.
WALTERS, W., GRAY, H. K., AND PRIESTLEY, J. T.: Malignant lesions of the stomach; importance of early treatment and end results. J.A.M.A. 117:II:1675–1679 1941.
WELCH, C. E. AND WILKINS, E. W. J.: Carcinoma of the stomach. Ann. Surg. 148:666–672. 1958.
WOLLUM, A., GLASER, D. F., BRYANT, H. C., AND POLLARD, H. M.: Cytologic study of the gastric aspirate for carcinoma cells: paraffin-block technic. J. nat. Cancer Inst. 12:715–721 1952.
ZAMCHECK, N., GRABLE, E., JANKELSON, O. M., SMALL, M., AND LO GAURO, A.: Cytologic method in the diagnosis and investigation of gastric lesions. Gastroenterology 29:588–595: 1955.
ZELDOWSKI, H.: Value of cytologic examination of stomach scrapings for early diagnosis of cancer of stomach. Pol. Tyg. lek. 13:1549–1553:1958.
ZEMANSKY, A. P. JR.: Examination of fluids for tumor cells; analyses of 113 cases checked against subsequent examination of tumor. Amer. J. med. Sci. 175:489–504:1928.

APPENDIX 2

Letter of enquiry to patients suspected of having gastric cancer

Out Patients Department,
University Central Hospital
of Helsinki

Helsinki ——/—— 1960

Dear Sir (or Madam)

In 195—, you were examined at our Department, and on the basis of the examinations you were suspected of having gastric cancer
In the course of the examinations, a cancer cell specimen was taken from your stomach.
Subsequently we have heard nothing about your condition, and we therefore *request information on your present state of health* It would be particulary valuable to know if you have had an operation because of your illness, and if so, in which hospital
Please accept our thanks in advance for the information which will be extremely helpful to us.

Kari Seppälä

Address

Letter of enquiry to patients not suspected of having gastric cancer

Out Patients Department,
University Central Hospital
of Helsinki

Helsinki ——/——, 1960

Dear Sir (or Madam)

In 195—, you were examined at our Department because of stomach trouble, and a cancer cell test specimen was taken from your stomach.
For this reason we now *request information on your present state of health.* We should particularly like to hear whether you still suffer from stomach trouble, whether you have undergone any gastric operations or whether anything suggestive of gastric cancer has been found.
Please accept our thanks in advance for the information which will be extremely helpful to us.

Kari Seppälä

Address

cells from cytological specimens C 19 gastric neoplasms classified according to the histolo μ of the neoplasm.

Scirrhous carcinoma patients							Tubulary carcinoma patients								Solid carcinoma patients									All cord carcinoma patients			
Cases							Cases								Cases									Cases			
14		22	23	21	25	26	15		16		27	28	29	30	17		18		19		31	32	33	34	35	36	37
B	C	B	B	B	B	B	B	C	B	C	B	B	D	B	B	C	B	C	B	C	D	B	B	D	B	B	B
2				18								3															
4				17			1					12									3				3	2	
35	12	17	1	21		2	7	2	1	2		21	9			3				1	25	1	5	4	9	16	1
23	19	21	11	25	4	9	32	15	8	9		42	31		2	26	3	1		1	32	10	33	15	30	13	15
35	43	36	30	12	9	27	31	40	34	19	6	11	21	21	22	23	23	5	2	7	31	18	30	8	38	29	39
5	13	17	19	6	23	35	14	28	28	9	20	8	21	30	28	20	41	8	7	19	8	21	26	17	17	20	31
1	3	10	19		23	18	11	10	21	6	20	1	7	23	34	11	70	40	9	27	1	27	6	27	5	15	11
			12		14	9	5	5	6	1	13	2	4	11	6	6	20	12	17	18		9		8	1	5	1
			5		13		1	3	1		22		1	7	7		12	12	12	10		8		7		1	
			4		4					1	12		2	2	1	1	5	7	1	3		5		12		1	2
									1		4		1	1	1		3	5	11	2		1		3		1	
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					1																						
8.3 μ 1							8.8 μ 10.5								9.2 μ 10.9												

REFERENCES

1. *Bauer H. J.* and *Gentz, C.* Acta Tub. Scand. 29:22, 1953.

2. *Bruce T.* and *Wassén E.*: Act Med. Scand. 104:63, 1940.

3. *Löfgren, S.* Act Med. Scand. 142:260, 265, 1952.

4. *Löfgren, S.* Acta Med. Scand. 145 424, 465, 1953.

5. *Löfgren, S.* Act T b. Scand. Suppl. 15 15, 1959.

6. *Schaumann, J.* Su le lupus pernio, Stockholm 1914 and 1934.

7. *Wallgren, S.*: Nord. Med. 60 1194, 1958.

8. *Wegelius, C.* and *Wijkström S.* Nord. Med. 60 1191 1958.

STATISTICS

In the present investigation conventional statistical methods have been used. Significance of differences between groups was tested by the t test. The methods of calculation were usually taken from Snedecor (1959). The degree of probability was designated as follows

$0.05 \geq p > 0.01$ probably significant

** $0.01 \geq p > 0.001$ significant

*** $0.001 \geq p$ highly significant

Table 1 Case reports in 11 patients with sarcoidosis (hilar lymphomas)

Case no. Examination period	Sex Age	History	Symptoms: First symptoms	Symptoms on admittance	Dyspnoea
1 Nov 1958	♀ 25	III-parae last delivery Oct. 57 Nursing until May -58 X-ray pos. Sept. -58 (Large BHL)	June 1958 sear [illegible] lling	10.9 58 EN and fever 3 weeks. Joint swelling and pain, tiredness effort dyspnoea	+
8 Jan. 1959	♂ 30	Throat infections before tonsillectomy -47 X-ray normal to May -58. X-ray pos. Nov -58 (Large BHL)	Nov 1958 EN Fever 6 week	EN Joint [illegible] lling and pain Fever	—
9 Feb. 1959	♂ 24	Throat infections before tonsillectomy -23. Small left pleurisy -53. Gallstone on X-ray 59. Lung X-ray normal to -54 X-ray pos. May -58 (Moderate BHL)	April 1958 thoracic stitch	Tiredness, thoracic stitch. Effort dyspnoea	+
20 April 1959	♀ 37	X-ray normal -48. EN Dec. 56 with BHL on X-ray decreasing to 58. New period with symptoms March -59 X-ray pos. March -59 (Moderate BHL)	Dec. 1956 EN joint swelling and pain	10.3 -59 EN Joint swelling and pain. Tiredness Effort dyspnoea	+
24 June 1959	♀ 32	I para (-49) BCG -50 and 57 X-ray normal to May 58. X-ray pos. March -59 (Large BHL)	March 1959 EN	EN Joint [illegible] lling and pain Ocular symptoms Thoracic stitch.	—
25 July 1959	♂ 24	Psoriasis from -48. X-ray normal to -57 X-ray pos. 6.4 59 (Large BHL)	Nov -58 tiredness. April 59 lymphgland swelling and fever 5 weeks	Fever lymphgland swelling, orthostatic complaints, tiredness thoracic stitch.	—
26 July 1959	♂ 20	BCG 58 X-ray normal (June 58) X-ray (routine) pos. May 59 (Large BHL)	—		
28 Sept. 1959	♂ 39	EN ? 27 Commotio cerebri -48 Nervous symptoms several years. X-ray -46-49 = Moderate BHL, decreasing to 54 X-ray (routine) pos. May 59 (Moderate BHL)		Effort dyspnoea and tiredness (several years)	+
29 Sept. 1959	♀ 21	II para last delivery Nov 58 Nursing to April -59 X-ray normal to April 58. X-ray pos. Aug. 59 (Large BHL)	Feb. 1959 tiredness weight loss	Orthostatic complaints, tiredness	
30 Sept. 1959	♀ 46	I para(33) From 51 pain in [illegible]. Cholecystectomy Aug. 58. Periods of bronchitis 53-59. X-ray normal to May -58 X [illegible] (routine) pos. M [illegible] 59 [illegible] BHL)		Tiredness and thoracic pain (-53-59)	
[illegible]	♀ [illegible]	[illegible] Nov -58, arising in Sept [illegible] nal to 49 Tiredness at [illegible] 52 X-ray 51 53 showed [illegible] normal, X-ray [illegible] Moderate BHL)	1949 EN?	Tiredness, thoracic stitch, effort dyspnoea, the same symptoms -49 -52 and 59)	

B[illegible] ne[illegible] [illegible]mation, BHL [illegible] lateral hila[illegible] lymph nodes, EN [illegible] erythema nodosum.

ACTA MEDICA SCANDINAVICA

SUPLEMENTUM 366

STUDIES ON THE CARDIOPULMONARY FUNCTION IN SARCOIDOSIS

Edited by
NILS SVANBORG

Cases with Bilateral Hilar Lymph node Enlargement and Radiographically Normal Lung

By ALF HOLMGREN and NILS SVANBORG

Cases with Parenchymal Infiltrations of the Lung but without Radiological Signs of Fibrosis

By NILS SVANBORG

Cases with Fibrosis of the Lungs

By NILS SVANBORG

ACCOMPANIES VOL 1 0

STOCKHOLM 1961

after mediastinoscopy in the mediastinum (16). The biopsy material and repeated gastric lavage were tested in guinea pigs for tuberculosis. The results were negative in all cases. All patients were hospitalized for at least two weeks, during which time the study was performed.

Methods for analyses of circulatory function

Electrocardiogram. ECG was recorded at rest in supine position, standing, during exercise in sitting position and after exercise in supine position. The following leads were used. At rest, I, II, III, AVR, AVL, AVF, CR, CR, CR, CR, and CR. During exercise the indifferent electrode was moved to the forehead (CH leads) (64) and CH, CH, CH, and CH were recorded. CH-leads have been shown to be approximately identical with CR leads except in cases with marked right ventricular hypertrophy or right bundle branch block (41).

BMR. Basal oxygen uptake was determined under standardized conditions by the Douglas-bag technique, 10 min periods, duplicate determinations. The expired air was analyzed for oxygen and carbon dioxide content with Haldane technique (25). The reproducibility of

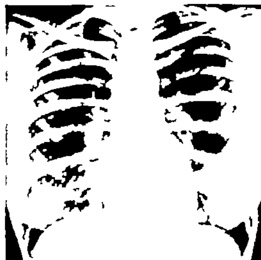


Fig. 1. Chest x-ray in Case 33 illustrating moderate bilateral hilar lymph node enlargement, exemplifying group I A in Table 1.

rate of or close to 170 beats/min was reached. Using the approximately linear relationship between heart rate and work load the value for W_{170} was then obtained either by extra- or intrapolation. A relative steady state was defined as being present if the pulse rate did not increase more than 10 beats from the second to the sixth minute on the highest load. To determine the heart rate response in supine position a similar work test, using the same series of loads was performed in this position.

From the Lung Clinic and the Medical Clinic II of St. Görans Sjukhus and
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STUDIES ON
THE CARDIOPULMONARY FUNCTION
IN SARCOIDOSIS

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(9) This investigator suggests that indices more than 10.4 would be likely to indicate impaired intrapulmonary mixing. The N_2-wash out time was determined with a reproducibility of 12%. Normal range has been reported to be 2.2—3.5 min and values above 4 minutes were regarded as pathological (14). FRC was determined with a reproducibility of 9%.

Bronchospirometry was carried out with Carlens (15) tube sizes 35—37 for the women 39—41 for the men. The patients were investigated in recumbent, right and left lateral recumbent and sitting positions, breathing into a closed system double spirometer filled with oxygen enriched air (69). The results are given as the mean value for oxygen uptake of all four examinations for each lung expressed in per cent of total oxygen uptake. Normal values, Right lung, 53.2% (range = 47.8—57.0%).

Diffusion and gas exchange. The pulmonary diffusing capacity for CO (D_{LCO}) ml STPD min/mm Hg was measured with the steady state method (23) with correction for the CO back pressure (51) in pulmonary capillary blood. Determinations were made at rest and during moderate exercise increasing the heart rate to an average of 143 beats/min (range 112—164). The procedure has been described earlier from this laboratory (51, 52). P_{ACO_2} was taken to equal P_{aCO_2} in the present group. The reproducibility of determinations of D_{LCO} averages 4—5% (51). Normal values for D_{LCO} were predicted from oxygen uptake and age with 4.3% at work (see above under BMR) (36, 40).

Venous admixture in the lungs due to an anatomical shunt was estimated as outlined by Berggren (10). Owing to the low degree of accuracy at high oxygen tensions (see under analytical methods) of the mercury drop electrode the patients were breathing 40% O_2 instead of 100% (8) for 20 minutes. Normal values for venous admixture using this technique are reported to be below 5.2 per cent of the cardiac output (7, 8).

Maximum voluntary ventilation, (MVV) (l/min, BTPS) was determined with a Bernstein spirometer (Kifa) (11). All subjects in the sitting position. Three determinations were made and the highest value was used. The determinations were made at three fixed respiratory rates viz. 40, 60 and 80 breaths/min the patient following a metronome and at a rate that the patient chose himself. Normal values for MVV_{free} were predicted from the equations 220.2—1.510 × age for men and 137.2—0.744 × age for women (age in years) (37). The reproducibility of MVV_{free} determination was estimated with the aid of the two highest values for each subject and was 1.5 per cent. Normal values for MVV_{40} (45) were predicted from the equation 180.2—1.28 × age for men and 102.5 + 0.32 × age — 0.014 (age)^2 for the women.

Maximum inspiratory and expiratory flow rate were determined from forced expirations into and inspirations from a Bernstein spirometer (11). The investigation was continued until three repre-

CONTENTS

monoxide combining power of hemoglobin Mean capillary carbon monoxide tension ($P_{\bar{c}CO}$) mm Hg wa calculated from S_{CO} (51)

Lactic acid concentration in arterial blood mE/l was determined spectrophotometrically (2) The standard error of a single determination at a concentration of 50 mg per 100 ml blood was 3 5 per cent (30)

Pyruvic acid concentration in arterial blood mE/l was determined spectrophotometrically (24) The standard error of a single determination of a mean con centration 0.287 mE was 1 84 per cent, n=101 Excess lactate (XL) mE/l, (42) was calculated from the formula

$$XL = (L_n - L_o) - (P_n - P_o) \cdot (L_o/P_o)$$

when L_o and P_o are lactate and pyruvate concentrations at rest and L_n and P_n are lactate concentrations during exercise

General procedure

The study was completed in two week during which period the pati nt was hospitalized. Th first week was used for clinical investigation classification of the disease and bronchospirometry During the second week the physiological examination took place Four work tests were performed Two, one in sitting and one in supine position for the estimation of the rate of work at pulse rate 150 and 170 beat min one in sitting position for the determination of alveolar gas ex chang and pulmonary diffu ion capa c ty nd finally in supine position for ng heart c theterization Only on work test was performed each day

Results

ECG f re t wa w th n the n rmal va riat n n 9 p at ent In n patient Case 20 l ght d t S T and T f the m] atic t n e t p t served (35) During and after the work test the ECG was normal in all patients.

B.M.R was on an average +6 % (range —13 +32) of the predicted normal value (20) In Case 28 (see case report) the BMR was +32 % a value which was verified repeatedly Thyrotoxicosis could be excluded however

Orthostatic test Two patients (28 and 33) showed a very marked increase in the heart rate to 120 and 130 beats/min respectively in standing position Five patients (2, 9 20 24 and 25) demonstrated a marked increase (≤ 119 beats/min) The other patients showed only moderate increases of the pulse rate (Table 2)

Total amount of hemoglobin was on an average 10 13 g/kg body weight (range 8.87—12.27) for the men and 8 11 g kg (range 7 07—9 09) for the women These mean values are statistically probably different (p =) from the normal values earlier reported from this laboratory (31)

Blood volume was on an average 78 9 ml/kg body weight (range 72.2—80.3) for men and 72.3 ml kg (range 62.5—88.6) for women Neither of these is statistically significantly different from the normal material earlier reported from thi laboratory (33)

Heart volume in prone position was normal in all patients, except Case 30 in relation to THb (31) Fig 3, i e twice standard error of estimate This patient was very fat (164 cm tall, 94 kg, woman, 40 years) but had no sign f cardiovascular disease pressure in b r ch al artery 130 75 mm Hg.

INTRODUCTION

Sarcoido is is a granulomatous disease or syndrome of unknown origin. The disease is characterized histologically by the presence of epithelold cell tu bercles most commonly involving the lymph nodes, lungs, skin, liver spleen, eyes, heart and kidneys The term sarcoidosis implies systemic involvement. Symptom and signs, when present, reflect the changes which have occurred in the tissues and organs involved but the features in the individual also depend on the extent of involvement and the stage in the development of the lesions. As the histopathologic signs which provide the basis for the variable clinical symptoms are non specific in type the cli nical criteria must be regarded as constituting th diagnosis of sarcoi dosis (5)

Medical awarenes of sarcoidosis has not been stimulated equally in the world, nor are the facilities for mass studies distributed ideally In Sweden, since the pioneering work of Schau mann 1914 (6) interest in the disease is great. For example in consequence of the studies of large sarcoidosis ma terials by Lofgren in 1946—60 the early stage has been well recognized and the clinical picture more fully described (3, 4 5)

Nation w de mass x-ray surveys were carried out in Sweden between 1930 and 1957 The prevalence rate for sarcoidosis was 42 per 100 000 inhabitants among the Armed Forces. In different counties of Sweden the corresponding rates varied between 7 and 140 The Stockholm series disclosed an incidence rate of 30 for men, and for women 50 100 000 inhabitants. In the age group 25—29 years, where the incidence is highest, the corresponding rates were 90 for men and for women 110 100 000 inhabitants (1 8)

The earliest report of ph siological studies in sarco dosis was that made by Bruce and Wassén in 1940 (2) From the literature abnormalities of cardiopulmonary function seem to be qu te variable possibly depending on the type localization and degree of the basic lesions. The aim of the present investigation was to study the functional pattern in different types of the disease

The clinical part of the investiga tion was performed at the lung clinic of St. Görans Sjukhus (Head Doc. S. Löfgren) and the physiological part at the department of clinical physiology of Karolinska Sjukhuset (Head Prof T Sjostrand) where Doc A. Holmgren helped with the methodology and planning of the investigation

Table 2 Some anthropometric data in 11 patients with sarcoidosis (hilar lymphomas)

Case no.	Sex	Age years	Height, cm	Weight, kg	BSA, m²	BMR, %	Heart V, ml	THb, g	THb/kg	Hb conc., g/100 ml
2	F	28	160	52	1.64	+10	680	465	8.93	13.2
8	M	30	181	68	1 71	+4	835	620	9 10	11.3
9	M	34	182	97	2 18	−8	1100	860	8.87	12.3
20	F	37	169	79	1 79	−2	740	660	8.35	9 9
21	F	32	164	72	1 78	+9	685	535	7 43	11.8
23	M	34	177	77	1.95	+21	730	765	9 95	13.5
26	M	21	183	75	1 94	+6	825	920	12.27	16 1
28	M	39	173	73	1.85	+32	845	765	10 48	12.2
29	F	21	170	44	1.60	+7	860	400	9.00	10.2
30	F	46	164	94	1 91	+2	1080	730	7 77	11.6
33	F	39	155	58	1.66	−13	610	410	7.07	11 1
♂ M		31 6	175.2	78 0	1 926	+11.0	867.0	786.0	10 13	12.88
range		21−39	161−183	68−97	1 71−2.18	−8−+32	730−1100	620−920	8.87−12.27	11.3−16 1
♀ M		33.5	162.0	66.5	1 680	+2.2	709.2	533 3	8 11	11.20
range		21−46	155−170	44−94	1.50−1 91	−13−+21	610−1080	400−730	7 07−9 09	9 9−13 2

BSA = body surface area THb = total amount of hemoglobin. BMR = basal metabolic rate in per cent of

to compare W sitting with a corresponding value in supine position W supine was calculated by extrapolation from the line obtained between

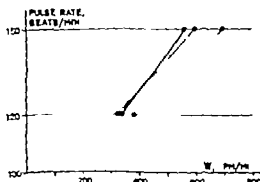


Fig 6 Pul ... rel tion ... tes) F 11 ... position, d ... sitting d ... ke line

120—150 beats per minute The calculated value for W_{70} supine thus obtained is uncertain and used only for the comparison with W_{70} sitting

Comparison between rate of work heart rate relationships in sitting and supine positions This comparison was performed as an analysis of the difference between $W_{..}$ and $W_{..}$ in sitting and supine position (Fig 6) W_{70} supine was on an average 52 kpm min higher than in $W_{..}$ sitting. This difference was however not significant ($p < 0.4$) At the higher pulse level $W_{..}$ supine was n an average 135 kpm min higher than $W_{..}$ sitting (p) The difference between heart rate n a given load in sitting and supine position was also te ted ... f p lse les l f from the

STUDIES ON THE CARDIOPULMONARY FUNCTION IN SARCOIDOSIS

I

Cases with bilateral hilar lymph node enlargement and radiographically normal lung

By

ALF HOLMGREN AND NILS SVANBORG

Pulmonary function in sarcoidosis of the lung has been studied by a number of investigators (17, 48, 67). Studies on the function in patients with hilar lymphomas without parenchymal infiltrations on x-ray are however scarce. In one investigation (48) a low arterial oxygen saturation was found in one case and in a series of five reported cases (17) one patient had reduced lung volumes and another a low diffusing capacity. All other tested functions were normal. In a third study of six cases with BHL without parenchymal infiltrations (67) lung volumes were normal in four cases and significantly reduced in two. Maximum breating capacity was not significantly changed. Hyperventilation was present during exercise and recovery in three cases. Three patients had increased alveolo-arterial O_2-gradients indicating abnormalities in ventilation-perfusion relationships.

The present report forms a part of a larger investigation on the cardiopulmonary function in sarcoidosis. In this report only patients with hilar lymphomas without parenchymal infiltrations on x-ray will be included. The study was planned to allow of a thorough analysis of the cardiovascular and respiratory functions and their integration in the solution of the oxygen transport and to analyse which part limits the oxygen transport if such a limitation was found. The oxygen uptake was varied with the aid of a bicycle ergometer and the significant parameters for evaluation of respiratory and cardiovascular function were studied both at rest and during exercise.

Material

The material consists of 11 cases with sarcoidosis of the hilar lymph glands, BHL, without any parenchymal infiltrations visible on x-ray. All significant data have been collected in a digested case report in Table 1, Figs. 1 and 2. In all cases the diagnosis was supported by biopsy of a lymph node in the supraclavicular fossa (19) or

Table 3 Observations during heart catheterization in 11 patients with sarcoidosis

Case no	Catheterization no.	Work load, kpm/min	Pulse rate beats/min	Oxygen uptake, ml STPD/min	Mechanical efficiency per cent	Ventilation, l (BTPS)/min	Ventilation, l (BTPS)/oxygen uptake, l (STPD)	O_2-capacity ml/100 ml	O_2-sat., per cent Br A	O_2-sat., per cent PA	AV O_2-diff ml/l	Cardiac output, l/min
2	66 58	rest	88	285		9.19	32.2	13.1	101	79	31	9.3
		200	121	683	24.1	20.71	30.2	14.0	100	52	69	10.0
		400	144	981	28.2	30.83	32.1	14.1	100	46	78	12.3
8	3 59	rest	92	306		7.49	24.5	15.9	98	76	37	8.3
		300	122	[illegible]	25.8	21.01	31.9	16.6	98	67	72	12.0
		600	152	1406	26.1	40.20	28.6	17.0	96	47	84	16.7
9	8 59	rest	78	343		9.31	27.1	16.6	101	78	39	8.9
		300	103	1059	20.0	24.33	23.0	17.0	96	55	74	14.3
		600	126	1532	23.7	37.36	24.1	16.9	97	48	84	16.1
		900	156	2223	21.7	61.36	27.6	17.5	97	39	102	21.9
20	37 59	rest	74	251		6.44	25.6	14.8	101	76	38	6.5
		200	125	824	16.8	22.12	26.9	15.7	101	61	66	12.6
		330	153	1072	20.3	33.54	31.2	16.4	102	58	73	14.7
24	56 59	rest	87	273		8.96	32.8	14.8	102	77	40	6.8
		200	124	825	17.4	23.24	28.2	15.5	98	52	82	10.0
		400	148	1196	20.7	36.61	30.7	16.2	99	47	88	13.5
25	57 59	rest	93	303		8.42	27.6	17.2	98	78	36	8.4
		300	117	914	23.5	[illegible]	27.4	18.0	98	59	72	12.7
		600	139	1639	21.5	43.73	26.7	18.5	97	49	91	18.0
		900	168	2362	20.9	72.20	30.6	18.8	98	38	112	21.0
26	58 59	rest	73	299		8.90	30.0	20.1	99	81	36	8.3
		600	126	1614	21.8	[illegible]	26.7	20.9	98	53	92	17.5
		900	148	2161	22.8	71.19	32.6	21.7	99	46	116	18.8
28	65 59	rest	84	360		10.05	27.9	15.9	96	74	35	10.3
		300	110	1151	18.1	29.50	25.6	16.5	9	53	70	16.5
		600	132	1712	21.2	47.97	28.0	16.7	97	48	84	20.3
		900	164	2444	20.8	[illegible]	28.9	17.2	94	37	103	22.8
29	69 59	rest	105	233		6.53	25.8	12.7	103	80	31	7.4
		200	160	63	17.9	21.69	25.4	13.5	100	55	65	13.2
		400	168									
30	71 59	rest	65	266		7.44	28.0	14.8	100	72	44	6.0
		200	94	[illegible]	13.9	[illegible]	23.6	15.6	100	48	82	11.6
		400	117	1262	18.8	34.43	26.8	16.3	99	47	86	15.0
33	60 59	rest	68	294		4.63	22.6	15.3	99	74	42	7.0
		200	123	748	21.1	18.11	24.2	15.9	101	60	82	9.1
		400	162	1134	22	34.65	30.6	16.2	101	40	100	11.4

Br A brachial artery PA pulmonary artery PCV pulmonary capillary venous pressure RA = right
XL = excess lactat

Reason for admittance		Clinical investigations				Time interval from, (months)			X-ray group	Clinical course after examination
Symptoms	X ray	SR mm hour	Mantoux	Electrophoresis g %	Other findings	Last normal lung x-ray	First path. lung x-ray	First symptom		
+	—	27	++	$\beta=1.0$ $\gamma=2.2$	Blood pressure 100/63 AS = 400		2	5	I B	X-ray unchanged 59. Improvement during 1960
+	—	103	++	$\alpha_I=0.6$ $\alpha_{II}=1.1$	AS = 400	10	2	2	I B	Improvement from April 1959
(+)	+	19	—	$\beta=1.0$ $\gamma=2.1$	Thymol = 8.0 AS = 800	60	9	10	I A	Unchanged during 1960
+	—	45	+	$\alpha_2=0.7$ $\gamma=2.5$	Uric acid = 7.7 Thymol = 7.0 AST = 2.8	156	27	28	I A	Improvement during 1960
+	—	39	+	—	AST = 2.8	13	2.5	3	I B	Improvement (Small parenchymal lesions) during 1960
+	—	62	—	$\alpha_1=0.5$ $\alpha_2=0.9$ $\gamma=2.0$	AS = 400	24	2.5	8	I B	Improvement (SR = 62–16 mm/hour 1959-1960)
—	+	4	—	($\gamma=1.6$)	Blood pressure 93/70 AS = 1000 AST = 2.0	12	1.5		I B	Improvement 1959-1960
—	+	15	—	Normal	—		156		I A	Slow improvement 1959-1960
+	—	40	—	Normal	Body weight 45 kg. White blood-cells in 8.5 eosinophils.	16	1	6	I B	Decrease of BHL but small parenchymal lesions 1960
—	+	18	—	$\gamma=1.9$	Weight = 92 kg.	16	4		I B	Decrease of BHL but small parenchymal lesions 1960
—	+	30	—	Normal	Uric acid 6.8	120 (16)	72 (7)	(120) (10)	I A	Improvement 1960 (Small parenchymal lesions?)

AS = antistreptolysin titer AST = antistaphylolysin titer

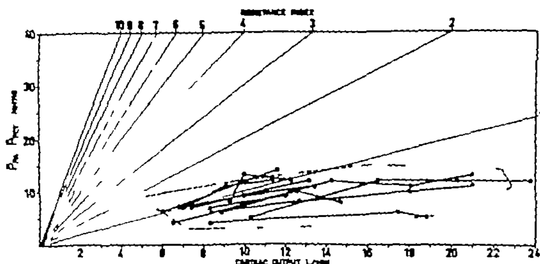


Fig 7 Press re gradient over pulmonary v scul bed, expressed the difference bet ween pulmonary rterial me press re ($\bar{P}_{PA}$) nd pulmonary capill ry venou pres ure ($\bar{P}_{PCV}$) i mm Hg (ordinat) i rel tion to rdiac outp t, l/min at rest and d ring erc se Hat hed re represent the norm l range found in this l borator (37) The obliqu lines are iso-resistance ind lines.

ther of the two cases could any signs of valvular lesions or myocardial In sufficiency be demonstrated The heart size was normal ECG normal at rest and during exercise and the stroke volume normal

Pulmonary arterial pressur varied within the normal limits at rest and during exercise compared with the normal material from this laboratory (3) The regre sion of mean pressure on pulse rat an be expressed by the equation y 0 01 x + 22 4 where y is mean p res ure in the pulmonary artery mm Hg, and x is heart rate beats/min Th r pressu n n t signi ficantly d fferent from that earlier found in a n r l material (3) The mean pres ned c nstant with increa in nt n ts

Pulmonary (pressed as

$$\frac{\bar{P}_{PA} \quad \bar{P}_{PCV}}{Q/m^2 \quad BSA}$$

was consequently normal at rest in all patients (range 0 93—2.60 units) (37) and decreased ordinarily during exercise in all cases (Fig 7)

Right ventricular pressures varied within the normal limits (37) During exercise the systolic pre sure increas ed to 50 mm Hg on the highest work load in cases 9 28, and 30 The end diastolic pressure remained on an average unchanged during exercise In Case 2 it increased from to 14 mm Hg during the first work l ad but fell t 10 mm Hg during the next load and pr bably does n t indicate myo cardial insufficiency During w rk a pressure gradient across the pulmo nary value up t 18 mm Hg (Case 28) be rec rded (37)

blood volume and disregarding the light u derestimation thu obt ined. N rmal alues with this m thod h v bee found to be 82 ml/kg SD 8.5 for men d 82 ml/kg S.D 13.0 for women (33)

Heart volume (ml) Heart volume wa d termined in th pron position ccord ing to Rohrer an l Kahlstorf modifi d by Larsson an l Kjellberg (47) u ing two pl n roentgenograms. The tand rd error of a singl determination d termined from duplicat determi ation mou ted t 4% (47 39)

Right heart catheteri ti n The procedure f r heart catheterizati i thi laborat ry h been reported earlier (31 33 30, 40) Blood ga lyses were performed spectrophometrically (36) Th errors i vol ed i the determin tion *of cardi output nd strok olum* i this l borat ry h been reported earlier (30, 39) The errors of singl determin tion f cardia output at rest were 8.2% and 5.2% duri g x rcise Corresponding figures f trok olum were 8 6 a d 6.8 per cent respecti ly

Methods for analyses of respiratory function

St tic lung vol n (l BTPS) Total lung capacity with its subdi i ions (61) were determi ed with the helium dil tion method usi g closed pirometer ystem (28) The ta dard error of i gl determi ati n of fu ction l residu l capacity wa 4% N rm l values for total lung capacity functional residual capacity residual volum and ital capacity were predicted from the formul reported by Grimby and Söderholm (27) These ormal lues ha been btai ed with th sam technique as i the present i estigation

V ntilati n ($\dot{V}_E$) l/mi BTPS w tudied t rest d during exercise using Dougl s-bag techniqu Expired ai was collected for 5 min t rest and for 3 min during e ercise The wo k wa perfor



Fig 2 Chest ray i Case 25 ill strating l rge bil teral hil lymph node enl rge me t emplifyi g group 1 B i T bl 1

med in sitti g position on bicycle ergometer The load wa hosen to i crease heart rate t erag of 150 beat min. Respiratory rate was determined during o mi t in the middle of the sampli g period. With th aid of arterial P_{CO_2} taken from th brachi l rtery in the middle of the sampling period *alveola ventilati n* was calcul ted from the for mul

$$\dot{V}_A(BTPS) = \frac{\dot{V}_{CO_2}\ (\ TPD) \times 863}{P_{aCO_2}}$$

sumi g no sig ifica t al eolo- rterial P_{CO_2}-gradients.

Di tribution of in pired gas was studied with th d on N limi ation cur ves d ri g oxygen breathing, using the Lilly N meter a modified by Lundi (14 54 55) d expressed as an index

$$\frac{\dot{V}_E\ (F_{EN_2}=2\%)}{FRC}$$ (9) and as N_2-wash-

out time to $F_{EN_2}=2\%$ (14) FRC wa determi ed as the N_2-space that had been washed out at $F_{EN_2}=2\%$ This wash-out i de could be determined with a reproducibility of 17% The t tal variation in n rmal material ha been found t be of the sam order 23% (7 02 S D ±1 68)

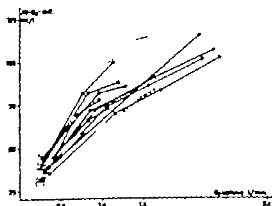


Fig. 10. Arterio- enous gen difference ml l, i relation t oxygen upt ke l STPD min. at rest nd d ring work. Symbol 1 Fig. 8.

within the same scatter of heart rate as in a normal material in all cases except patients 20 and 29 who both had low AVD in relation to heart rate during exercise see Fig 9 Highest observed AVD 110 ml/l at a heart rate of 148 and V_{O_2} of 2181 ml min (Case 26) Plotted against V_{O_2} (Fig 10) AVD varied within the normal limits except in Case 28 This patient, however worked longer than the others and at higher loads and the difference might be explained by direction of blood to the skin due to thermo-regulation

Oxygen uptake at rest during heart catheterization was significantly higher 33 % than under BMR conditions. During exercise V_{O_2} increased with increasing rat f w rk corresponding to a mechanical effic ncy of 18.8—28.2 on the highest w rk load, which varied between 200 900 kpm min (0 2.

Cardiac out ... nd cardiac index ...) (04 mean 3 0 ...

exercise Q increased linearily with increasing V_{O_2} with the same slope as in a normal material (12, 37) Fig 11

Stroke volume at rest expressed as stroke index, ml/m² BSA, was on an average 56 (range 40—67) in the male group and 53 (range 44—69) in the female group The stroke volume amounted on an average to 12.7 % of the heart volume and 1.74 % of the blood volume in the male group Corresponding figures for the female group were 13.30 and 2.08 % and for the whole group 13.01 and 1.93 %

On the transition from rest to exercise the stroke volume increased on an average 26 % of the resting value in 9 patients (Fig. 12) In two cases, 2 and 33, the stroke volume decreased markedly during the transition During continued work with increasing loads the stroke volume remained constant in four of the female patients

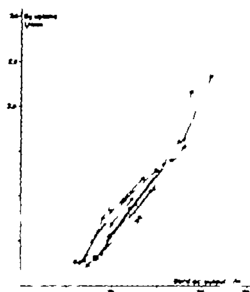


Fig. 11. Oxygen upt ke l STPD ml l re rdiac output l min. t rest nd k mbol Fig. 8.

l BTPS/sec nd FEV $_{1.0}$×100 VC, FEV %
The reproducibility of determination of FEV % wa estimated from th differe ces between the two highest alues l each subject and wa 3.5 per cent.

Pulmonary compliance l cm H$_2$O w let rmined from pressure- olume loop (21) Transpulmo ry pressure wa mea-sured a th pressure differe ce between oesophagus nd mouth wit a differen-tial manometer Volume w measured with a Krogh-spirometer The loops were plotted with a direct writing coordin t recorder (Elema) Determination were made duri g normal breathi g and du i g moderate volu tary hyperventilati The me of te loops was used The coefficiency of variation withi th n dividual was between 5—17 per cent that i f the same order s reported wit similar technique by Ehrne 1960 Normal range of variation with this tech-nique wa 0.14—0.39 l BTPS/ m H$_2$O i males and 0.10—0.25 l BTPS/cm H$_2$O i f males. The rati between complia d ri g resting co ditions a d during hyperventilati ra g d from 0.61—2.0 Compli ce during resti g conditio for both men and women was predicted from the formul 0.00405×(Height, cm)—0.595 S.D ±0.048 or 0.053×(V tal capa-city l BTPS)—0.035 S.D 0.042

T tal lung resistance cm H$_2$O/l/sec was det rmined from timed pressure volume loops ssuming the spirogram to be app-ro imat al usoid (21) Th m of 10 det rmi ti w used d the patie t was studied duri g ormal breathing and duri g moderat lu tary hyperventil tion Normal v lues with thi techniqu ary between 0.7—3.7 cm H$_2$O/l BTPS/sec *Ordinarily no signif ca t diff rence e i ts* between measurements m de during rest i g co ditions and duri g hyperventila-tion T t l lung resistance duri g hyper tilati n may be predicted f r both se es from th forced xpirat ry olum on second (22)

$$R_B = 840 \times \frac{1}{FEV_{1.0}} - 0.29 \quad SD = 1.00$$

Analytical methods

Analyses n blood samples Hemoglobin concentration (Hb.-conc) mg 100 ml wa determi ed spectrophotometricall as reported earlier from thi l boratory (30 60) with an error of a single deter min tion of 0.05 pe cent

Oxygen saturation (S_{O_2}) per cent, w d termined spectrophotom trically n hemolyzed whol blood (30) with n error of ingl d termi ation of 0.5 per ent.

Oxygen cont nt ol per cent, w s de-t rmi ed from th o ygen sat ration and the o ygе capacity of the blood sample calculated from the Hb-con using 1.34 for the o ygen combi i g power of hemo-gl bin.

Oxygen t n i n of art rial blood (P_{aO_2}) mm Hg was determined with the poten ti meter m thod for whole blood t 37 C usi g the mercury drop lectrode (4 5) In th high range of oxygen tension 500—700 mm Hg, the error of thi method i large (max±50 mm Hg) (4 5, 8) In th l w range (60—250 mm Hg) the error f a single determin tion is f the order of 3 per cent (8)

Carbon dioxid t nsi n of terial blood (P_{CO_2}) mm Hg wa obt ined from pH determi ti s in whole blood sing the H ea rel tionship between log. P_{CO_2} and pH (2) Measurements were m de at 37 C with glas lectrode The tand rd erro of pH determi ation w 0.002 u its (52) I the n rm l r ge f P_{CO_2} the error f pH det rm ti n was 0.002 unit Hg and at 20 mm Hg 1 mm Hg (52)

Stand rd bicarbonate mE/l, was det m ed s *the bicarbonat tent f plas-ma* f blood saturated with oxyge t 37 C d t a P_{CO_2} f 40 mm Hg (2)

Carbon monoxid co tent of art rial blood (C_{CO}) l per cent, wa deter mi ed by burning CO released i extraction chamber with KH (JO) with a H pealit CO-meter (Stålex) Th pe c t CO-saturati n S_{aCO} wa calcul ted from CO-co t nt and hemoglobi con centratio usi g 1.34 for the rbo

Table 4 Lung volumes 1 BTPS oxygen uptake of each lung in per cent of total (hilar lymphomas)

Case no.	IRV	TV	ERV	VC		FRC		RV	
				Obs., l	% of pred.	Obs., l	% of pred.	Obs., l	% of pred.
2	1 17	0.46	0 76	2.39	66	2.31	94	1.51	114
8	2.54	0 48	1.07	4.04	85	1 98	69	0.82	57
9	3.52	0 48	1.21	5.21	90	2.28	78	1.03	68
20	2 02	0.43	1 06	3.51	98	2.22	140	1.20	132
24	1 44	0 4	1 10	2.99	77	2.05	99	0.94	82
25	3.49	0.57	1.54	5 60	72	2.68	77	1.20	69
26	2.81	0.75	1 98	5.54	90	3.21	87	1.21	77
28	2.02	0 85	1 48	4.35	83	2.64	76	1.34	73
29	1.59	0.26	1.37	3.22	73	2.68	82	1.30	83
30	1.85	0.43	0.20	2.48	70	1 93	131	1 71	168
33	2.05	0.52	0 72	3.29	88	1.59	80	0 80	75
♂M	2.878	0 526	1 454	4 918	84	2.558	77	1 120	69
range	2.02–3.52	0 48–0.85	1 07–1 98	4.04–5.60	72–90	1 98 3.21	69–87	0.82–1.34	57 77
♀M	1.637	0 425	0 868	2 930	79	2.130	103	1.277	111
range	1 17–2.05	0.26–0 52	0.20–1.37	2.39 3.51	66 98	1.59–2.68	80–140	0.80 1 71	75 168

IRV respiratory reserve olume TV tidal olume ERV expiratory reserv volume VC = vital capacity

$\frac{V \ (F_{E_{N_2}} - 2\ \%)}{FRC}$ = nitrogen wash-out index

was 1 12 l BTPS or 69 % (p = *** of that predicted in the male group and 1.28 of 111 % of that predicted in the female group (p > 0.5) *Total lung capacity* was 6.08 l BTPS or 85 % (p = **) f that predicated in the male group and 4.26 l BTPS r 88 % (p < 0 1) of that predicted in the female group The quo tient residual volume t tal lung capacity was on an average 18.8 r 82 of that predicted in the male group and 30.2 or 120 f that predicted in the female gr up T summarize the male group w haracterized by mall p l (ties, mall p l l l nd mall l l

v lume The female group had a total lung capacity of the same relative magnitude as in the male group but an absolutely and relatively larger residual volume In two cases (2 and 30) the residual quotient was above what is considered the upper normal range 35 Case 2 had a low vital capacity and a small expiratory reserve volume Case 30 a very small expiratory reserve volume a moder ately enlarged functional residual ca pacity and an increased total lung resistance

Ventilation alveolar ga exchange pulmonary diffusing capacity blood gas ten ions and anaerobic metabo- l m were studied at rest in the upine

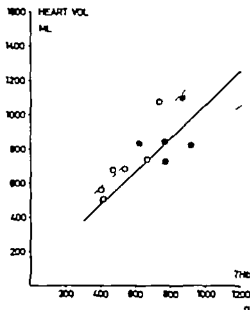


Fig 3. Heart ol me ml, (ordinat) i rela tion t total mount of hemoglobin (bs- cissa) Filled circles represe t m les nd open ircles females. Straight line repre sent normal regression line, described by Holmgren *et al.*, 1957 (21) Broken lines indicat ± standard error of estim t nd twice st ndard error of estimat

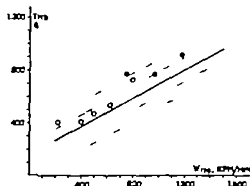


Fig 4 Total amon t of hemoglobin, g (or dinat) in relation t rat f work t pulse rate 170 beats/min. (W_{170}) kpm/ml (abscis- sa) in the sitti g position. Filled ymbols represent males nd open ymbol females. Normal *regression line* in *Fig.* 3.

nute To get an expres ion for the relationship between heart rate and the rate of work which could be used for a comparison with exercise in sitting body position, the rates of work at a heart rate of 150 and 120 (W_{150} and W_{120}) were calculated in each subject us ng the linear relationship between rate of work and pulse rate To be able

Working capacity sitting (W_{170} sitting) could be determined using the above given criteria in 10 patients. In all subjects W_{170} lay to the left of the regression line for the relationship between W_{170} and heart volume or total amount of hemoglobin (Figs. 4 and 5) In three patients W_{170} fell outside tw ce standard error of estimate and in three more outside one time stan dard error of estimate (p = **)

Working capacity in supine posi tion In the supine body position the patients as a rule could not perform work loads that increased the heart rate to or close to 1 0 beats per mi-

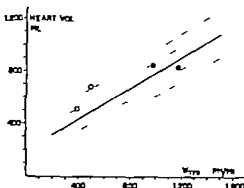


Fig. 5. Heart v l me, ml, (ordinat) in relation t rat of work at pulse rate of 170 beat /mi (W_{170}) kpm/min (abscissa) Symbols as i Fig. 3.

Table 5 Alveolar ventilation diffusing capacity and related values in 11 subjects with

Case no	Work load, kpm/min	Pulse rate beats/min	Respiratory rate breaths/min	$\dot V_E$ l BTPS/min	V_T, ml BTPS	$\dot V_{O_2}$ ml STPD/min	$\dot V_E$ l BTPS / $\dot V_{O_2}$ l STPD	RQ	Mechanical efficiency per cent	V_D/V_T	V_D, ml BTPS	$P_{a_{CO_2}}$ mm Hg
7	Rest	80	33	16.26	462	249	60.2	0 90		0 28	131	20
	300	134	42	34.01	810	848	41.0	0 98	24 8	0.24	194	30
8	Rest	70	20	8 66	433	299	29.0	0.81		0.36	151	42
	600	145	18	36.71	2039	1722	21.3	0 91	20 0	0 12	238	44
9	Rest	64	17	7.62	442	324	28.6	0 79		0.27	119	38
	600	126	17	33 93	1996	1758	23.8	0 94	20 0	0 10	200	39
20	Rest	82	18	6.88	382	218	31 6	0.83		0.26	101	38
	300	142	21	30.20	1438	1048	28 9	0 96	17.3	0 04	60	31
21	Rest	82	16	8 47	529	253	33.2	0.82		0 24	129	32
	600	148	22	36 10	1641	1293	27 9	0.91	23 0	0 09	141	32
25	Rest	76	11	7.65	693	299	25 6	0 75		0.2.	175	37
	600	124	20	38.81	1941	1547	24 9	0 92	22.6	0.14	271	38
	800	164	24	55.57	2315	1901	20.2	0.84	23.8	0 18	423	36
26	Rest	48	18	8 66	481	296	29 1	0 74		0.28	133	33
	1200	148	19	71 93	3787	3090	23 4	0.94	20.5	0 03	187	37
28	Rest	88	18	12.25	681	325	37 7	1.03		0 30	203	37
	900	162	27	51.29	1903	2722	18.8	0 90	18 0	0 03	53	43
29	Rest	82	15	8 28	419	225	27 9	0 71		0.30	128	27
	200	184	17	19 41	1142	697	27.8	0.92	20 3	0.23	268	39
30	Rest	74	18	7 77	432	238	30 0	0 80		0.28	124	37
	600	128	19	41 17	2167	1809	22.8	0 92	18.5	0.03	68	37
23	Rest	34	17	11.29	664	189	26.2	1 19		0 29	192	27
	400	112	21	42.76	2036	1340	31 9	0 99	17 2			24
Rest M Range		70.9 48 82	18.3 11 33	9 154 6.28 15 26	509 9 382 69.	267.5 189 325	32.6 25.6 60.2	0 85 0 71 1 19		0 28	144 4 101 203	34 8 20 43
Work M Range	582 200 1200	143 0 112 164	22.6 17 42	41.200 19 41 71 93	1934 0 810 3787	1646.2 697 3090	27.0 18.8 41 0	0 94 0 80 0 99	20.32 17.3 24 8	0.11	183 2 53 423	35.8 24 44

Symbols and abbreviations according to Pappenheimer *et al* Federation Proc 1950 9 602 M = excess lactate

Blood vol., l	Blood vol., ml/kg	Pulse rate standing, beats/min	W_{170} sitting, kpm/min	Highest load in sitting position				Orthostatic test Pulse rate at work		
				kpm/min	Duration of, min	Pulse rate beats/min	Resp. rate breaths/min	Load, kpm/min	Sitting beats/min	Supine beats/min
3.5	67.3	112	300	400	6	152	46	400	152	126
5.5	80.9	84	770	900	4	180	36	600	145	134
7.0	72.2	114	740	900	4	173	34	600	150	114
6.7	81.8	106	360	400	6	175	30	400	175	164
4.5	62.5	104	620	600	6	165	23	400	127	134
5.7	74.0	108	750	900	3	176	28	600	153	136
6.1	81.3	82	1175	1500	2	190	30	900	144	144
6.3	86.3	88	975	1200	2	183	46	600	130	140
3.9	68.6	120	220	400	2	183	24	200	161	148
6.3	67.0	76	800	800	2	160	30	400	115	122
3.7	63.8	130	400	400	6	171	20	400	171	140
6.12	78.94	95.2	882	1050		180.8	36.4	660	144.4	133.6
5.5–7.0	72.2–86.3	82–114	740–1175	900–1500		175–190	30–46	600–900	130–153	114–144
4.77	72.33	108.0	483	500		167.7	28.8	367	150.2	139.0
3.5–6.7	62.5–88.6	76–130	220–800	400–800		152–183	20–46	200–400	115–175	122–164

predicted. W_{170} = working intensity at pulse rate of 170 beats/min.

primary data and was found to be 7.43 beats per minute higher in sitting position. The probability that this difference is significant is almost of the same order as for W_{170} (p =). As mentioned above the working capacity in supine was also calculated as W_{170} and compared with W_{170} sitting. At this level the difference is 184 kpm/min (p = **) indicating a difference in slope for the two regressions.

Hemodynamic studies

Hemodynamic data obtained in connection with the heart catheterization are presented in Table 3.

Pulmonary arterial wedge pressure at rest lay within the normal variation in all patients (range 3—13 mm Hg) (37). When the mean pressure during exercise was plotted against heart rate the regression could be expressed by the equation $y = 0.007x + 0.9$ where y is mean wedge pressure in mm Hg and x is heart rate in beats/min. The mean pressure is 10 mm Hg at rest and does not increase significantly during exercise. This regression line does not differ significantly from that reported earlier for a normal material from this laboratory (37). In Case 25 a mean wedge pressure of 18 mm Hg was measured during exercise but did not increase further with increasing load. In Case 30 the resting mean pressure was 13 mm Hg and increased to 25 mm Hg during exercise. In nei-

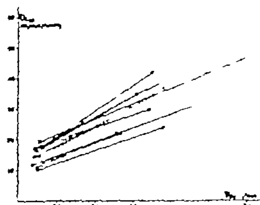


Fig 11 Pulmonary diffusing capacity for carbon monoxide D_{LCO}, ml STPD/min/mm Hg in relation to oxygen uptake ($\dot{V}_{O_2}$) ml STPD/min at rest in supine and during exercise in sitting position. Normal variation for this laboratory (63) indicated by broken lines.

tween dead space and tidal volume was 0.28 at rest and decreased to 0.11 during exercise (1). Case 2 had marked tachypnoe at rest with a normal V_D/V_T resulting in an alveolar hyperventilation, as is also indicated by the arterial carbon dioxide tension (20 mm Hg). Case 33 had also a marked alveolar hyperventilation, as indicated by P_{aCO_2} and RQ. In these two subjects alveolar hyperventilation persisted during exercise.

Diffusing capacity for carbon monoxide. The D_{LCO} at rest was on an average 15.6 ml STPD/min/mm Hg or 58 % (p = ***) of the predicted normal value. There was no significant difference between sexes. D_{LCO}/m² BSA was on an average 8.45 ml STPD/min/mm Hg/m² BSA or 63 % (p = ***) of the predicted normal value with no significant difference between the sexes. D_{LCO}/l BTPS mid-capacity of the lungs was 5.8. ml STPD/min/mm Hg/l midcapacity (p =) and no significant differences between the sexes (Fig 14). During exercise D_{LCO} increased in all cases to an average 30.1 ml STPD/min/mm Hg or 80 % (p = ***) of the predicted normal value at corresponding $\dot{V}_{O_2}$. D_{LCO} during exercise was higher for the men (8. %) than for the females (76 %). D_{LCO}/m² BSA increased to an average of 16.6 ml STPD/min/mm Hg/m² BSA or 85 % (p = **) of the predicted normal value with no significant difference between the sexes. D_{LCO}/l BTPS midcapacity increased to an average of 11.59 ml STPD/min/mm Hg/l BTPS or 101 % of the predicted normal value with no significant difference between the sexes.

To summarize the group is characterized by a significantly low D_{LCO} at rest, both absolutely and in relation to body surface area and midcapacity of the lungs. During exercise the D_{LCO} increases, but is still low in absolute terms and in relation to body surface area but normal in relation to lung volume.

Arterial oxygen tension. The average P_{aO_2} at rest was 86.6 mm Hg with a range of 74—96 values which lie within the variation of normal values in the literature and from this laboratory (32).

During exercise P_{aO_2} increased to an average of 91. mm Hg (range 80 — 103). In no case could a significant decrease be observed.

Arterial carbon dioxide tension. P_{aCO_2} at rest was on an average 34. mm Hg (range 20—43). In two cases (2 and 33) there were markedly de-

(hilar lymphomas)

Strok. volume ml	Lactic acid, mF l	Pyruvic acid, mF l	X.L., mF l	RA	RV		PA			PCV	BA			Pulm. vasc. resist. index
				M	S	De	S	D	M	M	S	D	M	
106	1.11	0.070		1	21	7	20	8	15	8	108	59	80	1.32
92	2.00	0.140	−0.22		44	14	33	17	25	12	135	70	99	2.00
85	3.03	0.190	0.03		45	10	35	19	25	14	140	70	93	1.30
91	0.78	0.070		−2	25	4	19	6	12	4	119	79	95	1.44
99	2.11				33	3	28	4	14	5	140	72	94	1.25
110	7.16	0.290	2.94		40	1	24	7	13		156	69	100	
114	1.06	0.065		2	27	2	27	7	18	7	127	70	92	1.47
140	1.94				35	4	33	13	19	11	147	75	100	1.03
144					46	0	42	13	24	8	150	71	100	1.32
125	8.16	0.260	1.03		52	1	43	20	27	11	170	[illegible]	106	1.29
88	1.11			0	18	7	16	9	12	7	125	72	94	1.10
100	2.33				34	7	30	13	20	13	135	71	100	1.42
97	3.44				39	2	33	9	17	8	148	74	106	0.97
78	0.89	0.093		0	33	8	18	11	15	8	119	67	88	1.83
81							32	18	21	12	135	65	94	1.60
91	2.55	0.140	1.24				28	11	20	9	132	72	96	1.78
90	1.50	0.125			21	9	16	7	12	8	130	80	96	1.39
108	2.83				38	6	30	16	22	18	138	71	88	1.23
130	3.93				42	8	35	17	25	18	137	86	114	1.05
125	8.99	0.295	3.46		45	5	35	31	28	18	160	90	124	1.02
114	1.44	0.070			21	4	14	6	10	6	116	68	90	0.93
139	5.88				27	2	21	9	12	6	118	55	82	0.67
127	6.16	0.310	0.23		34	8	19	5	11	6	143	81	105	0.52
123	1.07	0.090		−2	24	5	23	8	14	7	119	68	90	0.90
150	1.78				42	5	30	9	20	11	139	68	97	1.35
154	3.16				48	3	31	8	19	10	143	68	95	1.09
145	7.33	0.250	2.70		56	0	38	11	23	9	171	77	114	0.93
68	0.94	0.065		0	21	1	19	8	13	6	112	65	79	1.42
83	3.61	0.313	0.49		36	1	36	12	23	14	138	67	98	1.26
					42	3	35	13	24	14	140	72	96	
93	1.72	0.070		8	33	7	29	13	21	13	129	75	100	1.91
124	1.65				44	9	48	22	31	25	135	73	97	2.31
128	2.78	0.160	1.18		50	6	41	16	27		149	73	100	
103	1.22	0.060		3	23	5	19	6	11	3	131	71	92	1.58
73	2.17				34	0	31	9	17	3	153	73	100	1.89
70	4.61	0.192	0.69		42	1	30	8	14	6	164	78	108	1.64

atrium, S = systolic D = diastolic M = mean. Pulm. vasc. resist. index = $\frac{P \quad - P_{PCV}}{Q\ [illegible]}$

Table 6 Mechanics of breathing in 11 subjects with sarcoidosis (hilar lymphomas).

Case no.	MVV free			MVV 40		MVV 60 l/min	MVV 80 l/min	FVC, l		FEV 1.0, l	
	Obs., l/min.	rate	% of pred	Obs. l/min.	% of pred.			Obs. l	% of pred.	Obs., l	% of pred.
2 F	91	48	76	9	75	100	103	3.64	106	2 03	91
8 M	114	36	59	92	59	102	111	3.97	93	2.82	64
9 M	175	56	94	143	95	165	177	5.53	100	4 16	99
20 F	116	49	93	84	80	99		3.62	106	2.74	84
24 F	107	68	86	73	68	95	87	3.33	90	2.74	81
25 M	185	42	99	139	91	168	181	5 48	106	4.35	103
26 M	229	56	111	164	98	205	233	6.46	106	5 12	103
28 M	144	98	81	122	85	124	133	4 74	101	3.87	97
29 F	114	56	85	8	69	96	109	3.36	80	2 59	85
30 F	70	44	62	65	67	70	79	2.88	84	2.33	77
33 F	96	50	81	90	87	95	87	3.67	115	2.74	85
♂ M	160 4		89	121.8	86	152.8	187 4	5.24	101	4 07	93
Range	114—229		59—111	92—164	59—98	102—205	111—233	3.97—6.46	93—106	2.82 5 12	64 103
♀ M	98 8		81	78 2	74	93 0	92.8	3 40	97	2 73	84
Range	70—116		62—93	65—90	67 87	70—168	8 108	2.88—3.67	80 115	2 33—2 93	77 91

Maximum voluntary ventilation = MVV free MVV 40-60-80 breaths/min. Forced vital capacity = FVC, forced flow = MMF maximum midinspiratory flow = MMIF forced inspiratory volume in one second = FIV 1.0 FEV 1.0

breaths min an average volume change of 0.029 l BTPS and an intrathoracic pressure change of 5 43 cm H_2O Corresponding values during voluntary hyperventilation were 20.8 breaths/min, 1 16 l BTPS and 0 79 cm H_2O

Compliance The lung compliance during resting ventilation (Table 6) was, for the males, on an average 0 144 l BTPS/cm H_2O or 64.4 (p =) % of the normal value predicted from vital capacity Corresponding values for the females were 0 109 l cm H_2O and 90.3 % ($p > 0.4$) There was no significant difference between compliance during resting ventilation and hyperventilation

Total lung resistance The total lung resistance was 2 71 cm H_2O l BTPS sec (range 1 07—3.04) for men and 3.16 cm H_2O l BTPS sec (range 1 75—6.86) If 3 4 cm H_2O l BTPS/sec for men and 3.33 cm H_2O l BTPS sec for women are taken as the upper limit of the normal variation, (22) Cases 8, 30 and 33 fall outside these limits In Cases 8 and 30 lung compliance is also low which may indicate the presence of an increased tissue resistance

Maximum voluntary ventilation Maximum voluntary ventilation was determined at free respiratory rate and at three fixed rates, 40 60 and 80 breaths min The mean rate during determination of MVV free was 61.6 breath /min in the male group and 52.5 breaths min in the female group The values are presented in Table 6

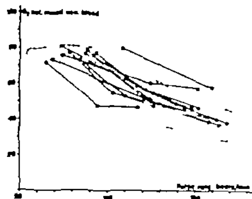


Fig. 8. Oxygen sat ration f mixed enou blood, per cent, rel tio t pulse rat beat per min. t rest nd d ring work, Normal range (Holmgren t al 1960) (37) i indi ted by broken lines. H tched rea repre sent resting values. Filled circles represent males nd open circles fem les.

Right atrial pressure was recorded normal at rest in 9 patients, and was omitted in 2 patients

Brachial arterial pressure was normal at rest in all patients and increased ordinarily during exercise (3) The relationship between arterial mean pressure and the heart rate at rest and luring exercise can be expressed by the equation = 0 16 x + 77 where y = mean pressure in mm Hg an l x heart rate in beat min This regression equation is not significantly different from the normal equation (37)

Arterial oxygen aturation was on an average 99.3 % at rest (range 96 —103) During exercise it decreased sl ghtly (30 37) but not significantly to 98 6 (range 94—102) At the same time the o ygen capacity of the arterial blood increased on an average 1.25 vol %. All values well within the normal variations.

Mixed venous oxygen saturation ($S\bar{v}_{O_2}$) varied between 2 and 81 % at rest, Fig 8 One patient (Case 29) had a sinus tachycardia at rest and $S\bar{v}_{O_2}$ fell outside the normal variation with heart rate (12, 3) During exercise $S\bar{v}_{O_2}$ decreased with increasing working intensity and heart rate In nine cases the relationship between $S\bar{v}_{O_2}$ and heart rate was normal In two cases, (20 and 29) $S\bar{v}_{O_2}$ was high in relation to heart rate during the second work load Lowest observed value 3" %. The results indicate that *in none of the cases has the hemodynamics been altered* ignificantly due to a low hemoglobin concentration

AV-O -difference (AVD) ml l at rest varied between 31 and 44 ml l *i e* within the borders of the normal variation earlier reported from this laboratory (12, 31 37) During exercise AVD increased with increasing heart rate with the same slope an l

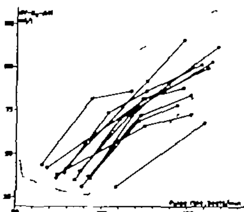


Fig. 9 Arterio- enous oxygen difference ml/l, in relatio t pulse rate, beat 'min. t rest nd during w rk. Symbol as i Fig. 8

predicted normal value in the male group and 81 1 % (p =) or 93 % of the predicted normal value in the female group

Maximum midexpiratory flow was 3 94 l BTPS/sec or 88 % (p = < 0.3) of predicted normal value in the male group and 3 15 l BTPS/sec or 76 % (p =) in the female group

Maximum midinspiratory flow was on an average 7.21 l BTPS per second in the male group and 4 09 l BTPS/sec in the female group

Forced inspiratory volume in one second was 4 76 l BTPS/sec in the male group and 3.08 l BTPS in the female group

$$\frac{FIV \times 100}{FVC} = FIV\ \%\ \text{was } 90\ 6$$

in the male group and 90 0 in the female group

Discussion

The present study of patients with sarcoidosis of the lungs was planned to allow of detailed analyses of the cardiovascular and pulmonary functions and of the integration of these functions for the solution of the oxygen transport at rest and during exercise

The material investigated forms a fairly homogeneous group, with a relatively short duration of the disease only three cases (20 28 and 33) have a probable duration of more than one year In these cases the hilar lymphomas are old, and vary in size on x ray and it is of course impossible to exclude period with parenchymal infiltrations. However on examination they do not differ from the rest of the group and have been treated with these The diagnosis was supported with mediastinal or supra clavicular lymph gland biopsy (16 19) in all cases The body dimensions were normal for both men and women. The dimensions of the cardiovascular system as expressed by blood volume total amount of hemoglobin and heart volume in prone position was slightly low but did not differ significantly from the normal materials in this laboratory

The rate of work that the patients could perform in sitting position at a pulse rate of 170 beats per minute W "sitting" was small both absolutely and in relation to heart volume and THb W ₁₇₀ supine on the other hand was markedly higher The low working capacity in sitting is in agreement with observations in patients with pulmonary tuberculosis (18) The central hemodynamics studied in supine at rest and during exercise was normal with regard to all parameters studied The stroke volume at rest was rather low in relation to the heart volume and blood volume On the transition from rest to work there was a significant increase of on an average 20 % of the stroke volume at rest This was a more marked increase than reported earlier from this laboratory in normal subjects of the same age (12, 37) The difference between the materials lies in the resting values. The present patients had a smaller stroke volume at rest in relation to body dimensions, probably due to an inadequate distribution of the blood

(Cases 2 20 30 and 33) and two of the male patients (Cases 9 and 28) The SV increased with increasing rate of work in one female (Case 24) and one male (Case 25) an l decreased in tw male patient (Cases 9 an l 26)

Compared with earlier result du ring exercise in the supine position (12, 37) the stroke volume blood volume varied within the normal range both at rest and during work It has been demonstrated that the reprodu cll ility of stroke volume determina tions is higher during exercise than at rest and that there exists a linear rela tionship between the stroke volume during exercise and THb (3) Plot ting the mean value for the stroke *volumes luring exercise* in an in divi lual in the present material (see Fig 13) showed that 10 patients fell within once the standard leviation Only one patient (Case 28) fell out side twice S D This patient had how ever a large stroke volume in relation to the THb. None had significantly low stroke volume during exercise

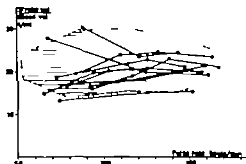


Fig. 12. Stroke al me divided by blood o l me, ml/l, in rel tion t pulse rat beats m t rest and d ri g work. Symbol as in Fig. 8.

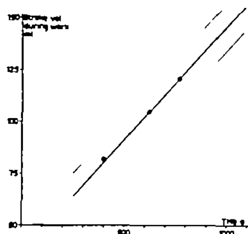


Fig 13. M l for ll observ tio of strok ol me d ring work in each ub ject, ml, i relation t t tal amount f hemoglobin, g. Straight lines indicate or mal regression between these parameters (*H lmgre et al 1960*) (37) ± st nd rd erro of estimat

Pulmonary function studies

Static lung volumes The results of the determinations of lung volumes are given in Table 4 The *vital capacity* was 4 93 l BTPS or 84 % (p =) of the predicted normal value in the male group and 2.98 l BTPS or 9 of predicted in the female group (p=**) The subdivisions of the vital capacity were in the male group *Inspiratory re erve volume* 2.88 l BTPS, *Ti lal volume* 0.63 l BTPS and *expiratory re serve volume* 1 46 l BTPS. Correspond ing figures in the female group were 1.69 0 43 and 0 87 l BTPS The *func tional residual capacity* was 2.56 l BTPS or 77 % (p = ***) of that pre dicted in the male group and 2 13 or 105 % of predicted in the female group (p > 0 9) The *residual volume*

decrease of the lung volumes it is important to consider the chosen material for prediction of normal values Swedish material investigated with the same technique (27) Even if the patients are compared with the normal material reported by Needham *et al* (60) the same significant types of changes remain The explanation of these changes is probably to be found in a combination of the effect of the expanding large lymphomas, parenchymal infiltrations and inactivity

The alveolar gas exchange was normal in all subjects as judged by P_{O_2} and P_{CO_2} at rest and during exercise which indicates fairly normal ventilation diffusion and perfusion relationships The anatomical shunt was of an order that is generally considered within the range of the normal variation

The mechanics of breathing wa impaired in eight of eleven patients, although not severely Four men and two women had a decreased lung compliance and two patients (Cases 8 and 30) increased total lung resistance Both these latter patients had decreased airflows (FEV and MMF) during maximal forced expirations indicating increased airway resistance Two of the patients with low lung compliance had increased total lung resistance which is not in general agreement with earlier studies (50) The decreased lung compliance is interpreted as indicating the presence of parenchymal infiltrations although not visible on x ray

Oxygen transport during exercise may be expressed by a series of equations for circulatory and respiratory functions If the work involves large muscle groups and is of an intensity high enough to increase V_{O_2} above 900 ml/min (70) the mechanical efficiency is fairly constant both within and between individuals (70 71) The mechanical efficiency may be expressed as

$$Me = \frac{W}{\Delta V_{O_2} \times 4.8 \times 427} \qquad (1)$$

where Me = mechanical efficiency W = rate of work kpm/min ΔV_{O_2} = increase in V_{O_2} due to exercise and 4.8 and 427 are constants for converting V_{O_2} and W to calories The oxygen uptake during exercise may be written as

$$V_{O_2} = W \times \frac{1}{Me} \times \frac{1}{k} = W \times k_W \qquad (2)$$

since the variation in resting oxygen uptake varies within narrow limits

The transport of oxygen by the circulatory system is expressed by the Fick equation

$$V_{O_2} = F \times SV \times (C_{aO_2} - C_{\bar{v}O_2}) \qquad (3)$$

where F = heart rate SV = stroke volume and $(C_{aO_2} - C_{\bar{v}O_2})$ = the arterio venous oxygen difference (AVD) The amount of oxygen that can be forwarded by the vascular system is consequently determined by the ability to increase heart rate maintain or increase stroke volume and extract oxygen

The work test used in the present investigation expresses the rate of work that can be performed at a pulse frequency of 170 beats/min, W_{170} which can be expressed by the equation

Nitrogen wash-out time min and N_2-wash-out index in 11 patients with sarcoidosis

TC		$\frac{RV}{TC} \times 100$		N_2 wash out time ml	$\frac{V}{FRC}$ (F_{N_2} = 2%)	O_2 uptake % of total	
Obs., l	% of pred.	Obs.,	% of pred.			Right lung	Left lung
3.90	79	39	156	1.6	6.8	48	52
4.91	78	17	71	1.8	7.9	55	45
6.24	86	17	81	1.8	7.7	54	46
4.71	110	25	100	1.2	5.6	67	33
3.93	80	24	96	2.3	8.4	69	31
6.80	93	18	75	2.8	6.2	53	47
6.75	87	18	90	0.9	5.5	47	53
5.69	81	24	92	2.5	8.2	56	44
4.72	79	32	139	3.2	6.3	48	52
4.39	94	41	146	3.0	8.7	54	46
4.09	94	20	83	2.3	6.3	44	56
6.078	*83*	*19.8*	*82*	*1.83*	*7.07*	*53.0*	*47.0*
4.91—6.80	78—93	17—24	71—92	0.9—2.8	5.5—8.2	47—56	44—53
4.257	89	30.2	120	2.23	6.98	55.0	45.0
3.90—4.92	79—110	20—41	83—156	1.2—3.2	5.6—8.7	44—69	31—56

FRC = functional residual capacity RV = residual volume TC = total lung capacity

position and during exercise in the sitting position The rate of work during this test was chosen to increase the heart rate to an average of 143 beats/min (range 112—164) Table 5 and V_{O_2} to 1656 ml/min (range 697—3080) corresponding to a mechanical efficiency of 20.3 The respiratory quotient increased from 0.85 at rest to 0.94 (range 0.89—0.99) during exercise

Ventilation During exercise V_E increased from an average of 9.1 l BTPS/min at rest to 41.1 BTPS/min (Tab 5) *The tidal volume* was on an average 11.20 % (range 8.5—15.7) of the vital capacity at rest in the male group and 16.42 % (range 10.9—20.2) in the female group During exercise the percentage increased to 48.4 % (range 38.3—68.4) in the male group and 52.4 % (range 33.9—87.4) in the female group The high value 87.4 was found in Case 30 who also had a low lung compliance and total lung resistance *The minute ventilation* was on an average 29.8 % (19.4—35.7) of MVV during exercise in the male group and 36.3 % of MVV (range 17.0—58.8) in the female group The *physiological dead space* calculated assuming $P_{CO_2} \approx P_{ACO_2}$ was 183.2 ml BTPS during exercise In four cases, 20 28 30 and 33 V_D decreased, indicating non steady state during the determination The relationship be

$P_{ACO_2} \approx P_{aCO_2}$ which is a reasonable assumption since no anatomical shunts of significance have been demonstrated. The efficiency of V_A can be expressed as the conductance of the airways for oxygen

$$\frac{V_{O_2}}{(P_{IO_2} - P_{AO_2})} \quad (9)$$

ml STPD/min/mm Hg,

which is better as it corrects for variations in V_{O_2}. This conductance was 3 . ml STPD/min/mm Hg at rest and 35.0 ml STPD/min/mm Hg during exercise values of the same order as can be calculated from normal data in the literature (53).

The diffusion capacity for *CO* was found to be low but the impairment is not of an order to explain the low working capacity as is also demonstrated by the alveolo-capillary oxygen gradients. These were calculated from equation 7 and averaged 14.9 mm Hg at rest and 43.2 mm Hg during exercise. These values indicate that there is still a diffusion reserve at the rate of work investigated (52, 53).

The observed value for AVD in sitting position was small in relation to the circulatory dimensions, indicating a small stroke volume or a low oxygen extraction. When the pulse response to increasing work load was studied in the supine position it was found that the same rate of work could be performed with a lower heart rate indicating a larger stroke volume or a higher extraction of oxygen. During heart catheterization normal values for stroke volumes, pressures and flows were found.

In an earlier series of studies on the effect of exercise in sitting and supine position on heart volume (39) and stroke volume (12) it was observed that heart volume and stroke volume were smaller during exercise in sitting position than in recumbent position, even in very well trained subjects (12). These studies also showed that the AVD was higher in upright position at a given V_{O_2}. The explanation that was suggested for this difference was that gravitational forces caused a pooling of blood in the veins of the legs and possibly in the abdomen, resulting in a decrease of the central blood volume and an impaired filling of the heart — a small stroke volume.

The present results seem to be compatible with these assumptions, as here the heart rate on a given load was higher in sitting position and from what is known of work in this position (12) the AVD should be higher than in supine position. In preliminary studies (38) it has also been possible to eliminate the pulse difference with the aid of an inflated g-suit during exercise in upright position. This "orthostatism" during exercise is probably caused by a lower than normal venous tone in upright position. Whether this is caused by the sarcoidosis or due to inactivity is not possible to decide at the time being.

From the above discussion it is obvious that the ability to transport oxygen in patients with sarcoidosis of the hilar lymph glands is not limited by respiratory functions. The somewhat low oxygen transport capacity seems to be due to circulatory factors in these patients.

sarcoidosis (hilar lymfomas)

P_{aO_2}, mm Hg	$\frac{Q_{sh}}{Q} \times 100$	$D_{L_{CO}}$ ml STPD min/mm Hg Obs.	$D_{L_{CO}}$ % pred.	$D_{L_{CO}}/m^2$ BSA Obs.	$D_{L_{CO}}/m^2$ BSA % pred.	$D_{L_{CO}}$/mid-capacity l BTPS Obs.	$D_{L_{CO}}$/mid-capacity % pred	pH, units	Standard bicarbonate mE/l	Lactic acid, mE/l	Pyruvic acid, mE/l	XL, mE/l
91		16 3	73	10.6	90	6.4	98	7.537	20	0.89	0.120	
84		23 6	90	16.6	114	10.1	117	7.363	18	2.29	0.263	0.43
90		17 7	64	10 4	71	8 0	101	7.393	23	1.00	0.073	
96		29 9	71	17.3	82	13 3	109	7.370	24	4.83	0.230	1 78
74	6 0	1 7	69	8.1	60	7.0	83	7.390	23	1 11	0.093	
96		42.1	106	19 3	98	16.7	139	7.244	20	4.00	0.215	1 18
79	3 7	14.2	51	7.9	66	5 8	87	7.389	21	0.94	0.070	
94		24.3	79	13.6	86	10.0	108	7.370	19	2.30	0 160	0 34
85	4.8	10 7	43	6 0	43	4 7	63	7 416	22	1 06	0 090	
92		22.0	63	12 4	67	9 6	89	7.333	19	2.94	0 163	1.01
86	4 4	17.3	67	8.9	64	5 8	78	7 430	24	1.33	0 030	
103		33.0	92	1 9	93	11.8	104	7.373	21			
103		37.8	92	19 4	93	12 7	102	7.337	19	4.33	0 230	0 71
84	4 0	19.3	58	9 9	56	5.4	60	7 423	23	0 83	0 033	
96		47 9	79	24 7	81	13.3	5	7.238	17	6.94	0.290	2.50
84	2 8	12.8	37	6.9	58	4.2	63	7 438	24	1 11	0 003	
80		34.8	73	18.8	82	11.3	78	7.265	18	5.27	0 220	2.39
95	2 6	17.0	32	11.2	63	6 0	68	7 438	26	1 06	0 093	
90		20.5	59	13.7	70	7.3	71	7 436	25	2.78	0 175	0 83
85	1 7	10.2	38	3 3	37	4 7	82	7 420	23	1.22	0 100	
62		23.9	86	12.5	76	11 1	105	7.244	20	1.83	0.193	−0.53
90	4.3	11.8	60	7.6	62	6.4	90	7.523	24	1 06	0.113	
94		22.1	77	14.2	86	11 9	119	7.500	21	4.03	0.210	2.16
86.6 74—96	3 02 1 7—6 0	15.00 10 2—19 3	58 43—73	8 43 3.3—11.3	63 43—90	6 83 4.2—8.0	80 60—101	7 438 7.389—7.537	23 0 20—26	1.035 0 83—1.33	0.098 0 003—0 120	
91.6 80—103		30.06 20.5—47 9	80 39—106	16 61 12.4—24 7	83 67—114	11.39 7.3—16 7	101 71—139	7.359 7.238—7.500	20 0 17—25	3.825 1 83—6.94	0.214 0 160—0.290	1 170 0 53—2.39

Q_{sh} = blood flow through anatomical shunt, Q = total pulmonary blood flow

22. *Fh n L.:* Acta Med. Scand., suppl 353 1960
23. *Filley G. F Macintosh D.J* and *Wright G W:* J Clin. Invest 33:530 1954.
24. *Friedman, T F* nd *Haugen G F* J Bi L Chem 147 415, 1943.
25. *Hald ne J S.* and *Priestly J G:* Cla rendon, O ford, 1935
26. *H rri J A* nd *Benedict F G:* Carnegie Inst. Wa h. Publ. No. 279 1919
27 *Grimby G* nd *Söd holm B.:* Perso l Comm nicatlons, 1961
28. *Holmgren A:* Scand. J Clin. & Lab. Invest 6:131 1954.
29 *Holmgre A* nd *M ttso K H:* Scand. J Clin. & Lab. Invest 6:137 1954
30 *Holmgren A:* Sc nd. J Clin. Lab. In est. 8 uppl. 24 1956.
31 *Holmg A J nsson, B Leonard M Lind rholm H Sjöstrand T* and *Ström, G* Act Med Sc nd. 158 413 1957
32. *Holmg en A* nd *Lind rholm H* Act Phy l L Sc nd 44.203, 1958.
33. *Holmgren, A Jonsson, B., Linderholm H Sjöstrand T* nd *Ström G:* Acta Med. Scand. 162:99 1958.
34 *H lmgr n A* and *Ström G* Acta Med. Sc d. 163 185, 1959
35. *Holmg n, A J son B., Leonard M Lind holm H Sjöstrand T* nd *Ström G:* Act Med Scand. 164:255 1959
36. *Holmgren A* nd *Pernow B* Scand. J Cli & Lab. I est 11 143, 1959
37 *Holmgren A J sson B* and *Sjöstrand T* Acta Phy lol. Sc nd. 49:343, 1960.
38. *Holmgren A* U publi hed observati ns, 1959
39 *H lmgre A* nd *Ovenf rs C. O:* Act Med. Scand. 167:267 1960
40. *Holmgren, A* nd *P rnow B.* Scand. J Clin. & Lab. Invest. 12:224, 1960
41 *Holmgren A* nd Strandell T Act Med. Scand. 169:57 1961
42. *Huck bee W F* J Clin. Invest. 37 244 1958.
43. *Kahl t rf A* Fortschr Rö tgenst 45 123, 1932.
44. *Kj llberg S. R Rudh l* nd *Sjöstrand T* Act R diol 31 113, 1949
45. *Kjellme I* Sandqvi t L nd *Bjrath G* Person l comm ic tions.
46. *Lagerlöf H* nd *W l l* Sc nd J Clin. & Lab Invest 1 147 1949
47 *Larsson H* nd *Kj llbe S R* Act Radiol. 29 159 1948
48. *Leit r & T J* d l st 10 379 1946.
49 *Lenall n E, C* nd *F wler W S.* Am. Rev Tuberc 72:783 1955.
50. *Lilly J C., And rson T F* nd *Hanrey J P* N ti nal Rese rch Council, CMR — CAM Rep N 299 1943.
51 *Linderholm H* Act Med Scand. 156 413, 1957
52. *Lind rhl m H:* A ta Med. Scand. 163:61 1959
53. *Linderholm, H* Cli ical Cardi pulmo ry Phy iology Grune and Stratton, 1960
54 *Lundin G* nd *Akesson, L.:* Scand. J Clin. & Lab. Invest 6:250, 1954
55. *Lundi G:* Scand. J Clin. & Lab. In est. 7:39 1955.
56. *Löfgren S:* Person l comm ic tion, 1961
57 *Löfgr n S.:* Act Med. Sc nd. 115 465 1943.
58. *Marshall R* nd *Duboi A B.:* Clin. Sci. 15 473, 1956.
59 *Marshall R Sm ill H Bayliss S H Hogl C* nd *Bates, D V:* Th ra 13 48, 1958.
60 *Needham C. D Rogan M C.* nd *M Don ld I* Thorax, 9:313, 1954
61. *P ppenh im J t al* Federation Proceed. 9 602, 1950.
62. *Sjö trand T:* Act Med. Sc nd Suppl 196, 687 1947
63. *Sjöstrand T* Act Phy l l Scand. 16 211 1948.
64. *Sjöstrand T* Sc nd. J Clin. & Lab I vest 3 1 1951
65. *Snedec C W* The Iow St t College Press, 1959
66. *St rn B* nd *Ström C:* Nord. Med. 7 243, 1957
67 *Ston P J Schwart A F llman J A* nd *Lovelock F J* Am. J Med. 15:168 1953.
68. *Sund man F W MacFat R P Mac Fadyen D A St son C F* nd *Cope land, R. E.* Williams nd Wilkins, Bal timore
69 *Svanberg L.:* Scand. J Clin. & Lab. I est. S ppl. 25, 9 1957
70. *W hlund H* Act Med. Sc nd. Suppl. 215 1948.
71 *Wikland O* Act Chi Sc nd 208 1954.
72. *Å trand P O* Experiment l tudies of phy ic l worki g capacity i relation to sex and g Munksgaard, 1952.
73 *Å trand I:* Act Ph iol. Scand 49 ppl. 169 1960

creased values, indicating alveolar hyperventilation In one case (24) a moderate alveolar hyperventilation was present

During exercise P_{CO_2} increased to an average of 35.6 mm Hg (range 24—44) In both Cases 2 and 33 the alveolar hyperventilation persisted during exercise In Case 24 P_{CO} remained unchanged

Anatomical shunt The anatomical shunt expressed as the venous admixture during breathing of 40 oxygen was calculated according to Berggren and Bartels *et al* from the formula

$$\frac{Q_{sh}}{Q} = \frac{C_c - C_{a_{O_2}}}{C_{c_{O_2}} - C\bar{v}_{O_2}}$$

The value for C_{O_2} was obtained during the heart catheterization. $\frac{Q_{sh}}{Q}$ and $C\bar{v}_{O_2}$ were assumed to remain unchanged during oxygen breathing (7 8) The flow through this shunt was on an average 3.6 % (range 1 7—5 0) or within the normal variation (7 8)

Acid-base balance The pH was on an average 7 438 units (range 7.389—7.537) at rest or within the normal range of variation During exercise pH decreased to an average of .350 units (range 7.258—7.500) Standard bicarbonate at rest wa 23 mEl, range 20—26 and decreased during exercise *to an average of* 20 0 mEl (range 17—25)

Anaerobic metabolism The lactic acid concentration at rest was 1 0 mEl (range 0.83—1.33) which falls within the norm l range of variation in the literature and from this laboratory (34) The pyruvic acid concentration at rest was 0 088 mEl (range 0.005—0 120) also within the normal range of variation (42) During exercise lactic acid concentration increased ordinarily with pulse rate to an average of 3.825 mEl (range 1.83—6 94) while pyruvic acid increased to 0.214 mEl (range 0 160—0.290) The resulting excess lactate was on an average 1 1 0 mEl (range 0.55—2.59) The figures indicate an ordinary amount of anaerobic metabolism during the rates of work investigated

Bronchospirometry The bronchospirometric data are presented in Table 4 as V_{O_2} on each lung in % of total The V_{O_2} of the right lung was on an average 53 (range 4 —56) in the male group and 55 % (range 44—60) in the female group In Cases 20 and 24 the V_{O_2} of the left lung wa lower than ordinarily found in a normal material investigated with the same technique (60) These two subjects increased the ventilation of the left lung in the left lateral position but the V_{O_2} was still low

Nitrogen wa h-out time was on an average 1.03 minutes (range 0.9—2.8) in the male group, and 2.23 min (range 1.2—3.2) in the female group All cases fell within the normal variation (14)

Nitrogen wa h-out index $V_E (F_{E_2} = 2 \%)$/FRC was on an average 7 07 range (5.5—8.2) in the male group and 6.98 (range 5.6—8 7) in the female group All cases were within the normal variation (9)

Compliance and total lung resistance were determined both at rest and during voluntary hyperventilation Resting values were obtained at an average respiratory rate of 20 7

Table 1 Case reports in 11 patients with sarcoidotic lung infiltrates.

Case no. Examination period	Sex Age	History	Symptoms		
			First symptoms	Symptoms on admittance	Dy p noe
12 Feb. 19 9	♀ 21	BCG 1946 Polio? 1942. X ray normal to M rch 1958 X ra (routine) pos. Dec. 1958 (BHL nd few parenchymal densities)	Dec 1958 Joint pain thoracic tlich tiredness	Orthostatic complai thoracic stitch tiredness	—
28 Feb. 1960	♀ 33	BCG 1944 X-ray normal to Feb. 1957. X ray (routine) pos sept. 1959 (BHL and few parenchymal densities) Unchanged to Feb 60)	Oct. 1959 Tiredness	Tiredness	
18 March 1060	♂ 29	BCG 1944 and 1948 Gastric ulcers 1951 56 X-ray normal to 1950 X-ra (routine) pos Jan. 1956 Epidymitis 1958 of unknown etiology (Guinea pig test neg) X-ra 1956-59 Slowly increasing lesions in both lunges			
27 Aug 1959	♀ 32	H-paree (1949 1951) Amenorrhoea fter operation for ovarial cyst 1953 X ra normal to March 1958 X ra (routine) pos. Apr 1959 (BHL nd moderate parenchymal densities)	1 1 1958 Sen w lling	Orthostatic complaints, thoracic stitch tiredness	
23 M 1959	○ 24	Period of gastritis 1949-51 X ray normal to May 1955 X ra (routine) pos. March 1956 (BHL and parench mal densities) 1956-60 increase of parenchymal densities			
21 Apr 1959	○ 49	X-ra normal to Nov 1955 X ray (rou tine) pos. Dec 19 5 (moderate parench mal densities in both lunges)			
11 Feb 1959	♂ 32	Poliomy litis without paresis 1936 Slight psoriasis X ra normal to Sept 1958 X ra pos Dec 1958 1958-Apr 1959 increasing parenchymal densities in both lungs decreasing BHL	Oct. 1958 12 Joint pain nd fever three week	Joint pain, tiredness effort d pnoea	
19 Apr 1959	○ 44	EN 1947 nd thereafter 31 tears pos t ents 1955 X ra 1945 Feb 1958 sho ed alethe tions X ra (routine) pos Feb 1959 (parench mal densities in both lungs increasing to Nov 1959)	April 19 5 Fever 4 d cough 3 months	Orthostatic compla ts, effort d spnoea	

BCG Calmette ... BHL bilater l hilar lymphnodes EN erythema nodosum, SS ... enlarged ...

FEV		MMF		MMIF l sec	FIV l	FIV₁	Compliance l cm H_2O	Compliance of predicted from height	Compliance of predicted from VC	Resistance cm H_2O l sec
Obs.,	% pred.	Obs., l/sec	% of pred.							
81	91	3 03	87	4 63	3 4	93	0 138	93	150	2.59
71	88	2 09	43	6 83	3 91	98	0 096	62	54	3.94
75	93	4 20	98	6 03	3.04	91	0.113	46	48	2.44
76	88	3.15	81	3.76	3.12	86	0.126	93	90	1.89
82	93	3.13	74	2.82	2.58	77	0.102	61	83	2 83
79	100	4 56	107	7.50	4 62	84	0.171	75	63	2.22
79	91	4 75	86	10 67	6 33	98	0.137	54	63	2.6[illegible]
82	103	4 11	103	4.98	3 90	87	0 201	96	102	1.97
92	100	4 91	100	4 75	2 89	88	0 066	44	63	1.35
81	98	2 32	70	4 00	2.99	100	0.032	31	54	6 86
73	87	2.06	53	4 60	3.43	94	0 141	112	102	3.41
77.2	95	3.94	88	7 21	4 76	90 6	0.144	66.6	64 4	2.708
71—82	88—103	2.09—4 73	43 10[illegible]	4 98 10.67	3.90—6 33	84 98	0.96—0.201	46—96	48—102	1 9[illegible] 3 94
81 1	93	3.13	76	4.09	3.09	90 0	0.109	72.7	90.3	3.153
73 92	87 100	2.06 4 91	53 100	2.82—7.50	2.58 3.47	77—100	0.52—0.141	31 112	54—150	1.35—6.86

[illegible]xpiratory volume in one second = FEV, FEV In per cent of FVC = FEV%. Maximum midexpiratory [illegible] in per cent of FVC = FIV%. Volumes in l BTPS, time in seconds.

MVV_{free} was 169.4 l/min or 89 % ($p > 0.2$) of the predicted normal value for the male group and 98.8 l BTPS/min or 81 % ($p = **$) of the predicted normal value for the female group. MVV_{40} was 131.8 l BTPS/min or 86 % of the predicted normal value in the male group and 78.2 l BTPS/min or 74 % of the predicted normal value in the female group. The observed MVV_{40} was significantly lower ($p = ***$) for the whole group than the predicted normal value. MVV_{40} and MVV_{40} were 152.8 and 167.4 l BTPS/min in the male group and 93.0 and 92.8 l BTPS/min in the female group. MVV_{free} consequently gave the highest value in this series, and there was no decrease of MVV with increasing respiratory rate which is in accordance with the normal compliance and resistance — time constants — observed.

Forced vital capacity. FVC was on an average 5.24 l BTPS or 101 % of the predicted normal value in the male group and 3.40 l BTPS or 9[illegible] % in the female group.

Forced expiratory volume in one second. FEV was on an average 4.0 l BTPS or 93 % ($p = < 0.3$) of the predicted normal value in the male group and 2.75 l BTPS or 84 % ($p = ***$) of the predicted normal value in the female group.

$$\frac{FEV \times 100}{FVC} = FEV$$ was 7.2 % ($p = > 0.2$) or 96.0 % of the

Case no. Examination period	Sex Age	History	Symptoms		
			First symptoms	Symptoms on admittance	Dyspnoea
3 Feb 1960	♀ 58	I para (1931). U eri 1936. Small left pleurisy 1937 Mantoux — + Skin tuberculids 1949 Cholecystectomi 1950 X-ray normal 1940 Feb. 1957 X-ray pos. Dec. 1959 (Marked parenchymal densities in both lungs).	M 1959 Iritis. July 1950 scar swelling	(Orthostatic complaints since youth). tiredness effort dyspnoea	+
14 Feb 1959	♀ 46	I para (1947) Cholecystectomi 1950 X-ray (routine) pos. Oct. 1954 (BHL). Improvement to 1958 but then increas- *ing infiltrates in both lungs.*	1954 Effort dyspnoea tiredness *1958 increase of symptoms.*	Thoracic pai tiredness effort d pnoea	+
5 Dec 1958	♂ 42	Epiphysiol sis right hip 1932. Left pleurisy (tbc) 1942. X-ray normal 1945-55 (Mantoux) X ra pos. N 1958 (BHL and marked parenchymal densities in both lungs).	M y 1958 Cough tiredness effort dyspnoea	Orthostatic complaints tiredness effort dyspnoea	

Table 2 Some anthropometric data in patients with sarcoidotic lung infiltrates

Case no	Sex	Age years	Height, cm	Weight kg	BSA, m²	BMR,	Heart vol ml	THb g	THb/kg	Hb conc. g 100 ml
12	F	29	173	59	1 71	3	590	585	9 92	12 5
38	F	34	161	56	1.58	13	545	440	7.86	10 2
56	M	31	176	56	1 72	8	430	645	11.52	12.9
27	F	33	170	71	1 82	1	890	620	8 73	11.2
23	M	32	1 3	85	2 00	− 11	900	850	10 00	14.2
21	M	50	1 8	66	1 85	− 15	800	615	9.32	13.2
11	M	43	17	62	1 77	15	570	535	8 62	10 5
10	F	44	160	58	1 58	14	680	530	9 18	12 6
37	F	[illegible]	1 3	68	1 82	5	685	500	7.35	10 8
14	F	[illegible]	1	54	1 52	19	660	465	8 61	11 8
5	M	42	185	90	2 18	12	1030	915	10 16	14 5
♂ M		3	1 8	3 4	1 904	8 8	786 0	718 0	9 926	13 06
Range		31	1 1	56 1	1 72 2 18	8 15	570 1030	535—915	8 62 11.52	10 5 14
♀ M		40	1	61	1 672	7 8	675 0	526 7	8 658	11.59
Range		29	1 1 1	4 1	1 2 1 82	3 19	1 890	440 620	7.35 9 92	10 2 – 12 6

BSA body surfac I IR basal metabolic rat in percent of predicted. THb = total amount of hemo-

volume. When the work was started the blood was redistributed, the central blood volume and the stroke volume increased. However, it was not possible to exclude the effect of a change in myocardial contractility resulting in an increase of stroke volume and decrease of residual volume. During continued exercise with constant or increasing loads the stroke volume remained constant, which is in accordance with earlier results reported from this laboratory (1[illegible], 3[illegible]).

Pulmonary function in patients with hilar and mediastinal adenopathy has been studied earlier (1[illegible], 48, 6[illegible]) but only in small series. In these studies the physiological findings were essentially within the normal range of variation. In one material (48) a low arterial oxygen saturation and slightly reduced maximum breathing capacity was found in one patient. In the other series (17) reporting five cases of hilar node enlargement but clear lungfields, one patient had reduced lung volumes, and another a low diffusing capacity. Apart from this, all pulmonary function tests, lung volume, ventilatory efficiency, diffusion and mechanics of breathing were normal.

In the present material the static lung volumes were significantly smaller than the predicted normal values. The decrease affected both residual volume and vital capacity in the male group but only vital capacity in the female group. The ventilation of the lungs at rest and during moderate exercise was normal in most cases. In two cases, however, a significant alveolar hyperventilation was found both at rest and during exercise. This does not indicate a permanent alveolar hyperventilation (6[illegible]) since standard bicarbonate was within the normal variation in both cases.

The diffusion capacity for CO at rest in supine position was low in relation to the predicted normal value both in absolute terms, in relation to body surface and to observed pulmonary midcapacity. The diffusion capacity during exercise in upright position was also smaller than predicted, both in absolute terms and in relation to body surface area, but normal in relation to the observed lung midcapacity. The relationship between D_{LCO} and midcapacity of the lungs might indicate that D_{LCO} is decreased, due to a diminished diffusion surface. The D_{LCO} during exercise was determined in sitting position and a decrease in capillary blood volume due to large orthostatic blood volume shifts seems to be a reasonable assumption. The hemoglobin concentration was normal in all cases and is thus not a factor which could explain the decrease in D_{LCO} in this material.

The group was selected with the criteria that no parenchymal lesions should be visible on x-ray. This does not exclude such changes, which is illustrated by the fact that parenchymal sarcoidosis has been observed in lung biopsies from BHL cases without parenchymal changes on x-ray (56, 57).

The small total lung capacity was a result of a decrease in vital capacity and a decrease of the residual volume. To evaluate the significance of this



Fig. 1. C 12, 21/2 1959: Right parat he l nd BHL. Som di cret milliars den lties l both l gs.

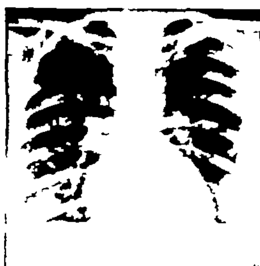


Fig. 2. C 39 10/2 1960 BHL nd m mill ry de lties l both l gs.

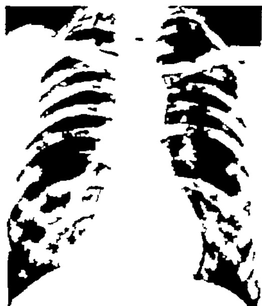


Fig. 3. C 16 21 19 9 Some mil ry den ties l l th l g P t h d lties l the ppe p rt f the l gs.



Fig. 4. C 27 21 8 19 9 BHL, mil ry nd some nod l den lties l both l g

$$\frac{W}{170} = SV \times AVD \times \frac{1}{k_x} \qquad (4)$$

This work test thus gives an approximate value for the product of stroke volume times oxygen extraction "the oxygen pulse" It is immediately obvious that W is determined by the size of the stroke volume and the degree of oxygen extraction The size of the stroke volume is primarily determined by the dimensions, the filling and the emptying of the ventricles The AVD is determined by the relationship between Q and $\dot{V}_{O_2}$ in various tissues. Low values for W due to small dimensions, impaired filling and emptying of the ventricles and to an overperfusion of the body — low AVD — have been reported in a series of studies from this laboratory (31 33 37) Studies of the relationship between stroke volume and W_{170} (37) have demonstrated a linear relationship with a rather narrow scatter indicating that the interindividual variation of AVD at a given $\dot{V}_{O_2}$ is fairly small The stroke volume has also been found to be correlated to the heart volume (37) and to the THb (37) These correlations between SV and W and SV and the dimensions of the vascular systems explain the repeatedly demonstrated linear relationship between W on the one hand, and THb and heart volume on the other (44)

The relationship between the gross ventilatory function and oxygen uptake may be epressed by the equation (53)

$$\dot{V}_{O_2} = \frac{\dot{V}_A (P_{I_{O_2}} - P_{A_{O_2}})}{P_B - 47} \qquad (5)$$

indicating the possible limitation of the $\dot{V}_{O_2}$ and consequently the rate of work that can be performed with impaired alveolar ventilation

The relationship between $\dot{V}_{O_2}$ and the diffusion capacity of the lungs is expressed in the diffusion equation

$$\dot{V}_{O_2} = D_{L_{O_2}} (P_{A_{O_2}} - P_{c_{O_2}}) \qquad (6)$$

A low $D_{L_{O_2}}$ indicates the presence of a high alveolo-capillary oxygen gradient This gradient may be calculated from D_{LCO}.

$$(P_{A_{O_2}} - P_{c_{O_2}}) = \frac{\dot{V}_{O_2}}{1.23 \times D_{LCO}} \qquad (7)$$

The integrated cardio-pulmonary function during exercise may be studied with the aid of equations 2, 3, 5 and 6 as summarized in equation 8.

The present investigation has shown that in patients with hilar lymphomas due to sarcoidosis, alveolar ventilation is not impaired at rest or during exercise This is expressed by the value for the mouth alveolar oxygen gradient in eq 8 which averages 48.5 mm Hg at rest and 46.5 mm Hg during exercise $P_{A_{O_2}}$ is calculated from the alveolar gas equation assuming

$$k_{\infty} \times W = \dot{V}_{O_2} \begin{cases} \dot{V}_A \dfrac{P_{I_{O_2}} - P_{A_{O_2}}}{P_B - 47} & \text{Ventilation} \\ D_{L_{O_2}} (P_{A_{O_2}} - P_{\bar{c}_{O_2}}) & \text{Diffusion} \\ F \times SV \times (C_{a_{O_2}} - C_{\bar{v}_{O_2}}) & \text{Cirkulation} \end{cases} \qquad (8)$$



Fig. 7 a. C 11 20/1 1959. Moderat mill ry nd fl lines de ities l both l gs.

Fig. 7 b. C 11 6/4 1959: From J ry 1959 increased, ow ma ked mill ry den i ties l both lu gs.

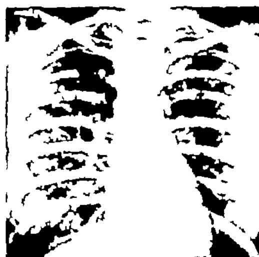


Fig. 8. C 19 2/4 1959. M rked miliary nd nod la partl oalescent p t hy den ities in both l gs.

I ilateral hilar lymph nodes (BHL) have been rep rted (22). Thi report deal only f p t nt with parenchy mal infiltr tes but without signs f fil rosi . The fin i n in cases with pulmonary fil rosis will be lescribed in a f llowing paper.

The study was planned to allow an analysis of pulmonary an l cardi vasculars dimensions and functions and to investigate whether the disease limit the oxygen tran p rt.

Material

The material con i ted of five men an l six women a lmitted to the lung clinic at St. G ran Sjukhus (Case 14 was at the medical th racic clinic of Karo lin ka Sjukhuset). The patient had a mean age of 39.4 (range 20—58) years an l all ha l sarcoi l tic lung lesi ns of different degrees but with out signs of fibrosis on x ray (16, 17). All significant data have been collec ted in a digested case report in Tal le 1. In all case the diagnosis was sup ported by l i p y f lymph nodes fr m

Summary

1 11 patients men and 6 women with sarcoidosis of the hilar lymph glands, but without parench mal in filtrations on x ray were investigated with series of cardiopulmonary func tion tests, allowing an a lequate eva luation of cardiovascular and pulmonary function separately an l the in tegration of these functions for the solution of the oxygen tran port.

2. The dimensions of the circulatory system, as expressed by l lood v lume t tal amount of hemoglobin an l heart volume were not significantly different although lower than in a normal material

3 The rate of work that could be performed at a pulse rate of 170 beat min was lower than pred cted from the circulatory dimension in the sitting position In supine position the pulse rate on a g ven load was lower than in sitting. These changes are regarded as being lue to a low stroke volume in sitting position owing to gravitational shifts of the central blood volume

4 The cardiovascular function at rest and during exercise studied with right heart catheterization was nor mal in all cases

5 Static lung volumes were rather low in eight cases, ventilation normal in all patients Lung compliance wa decreased in six patients and total lung resistance was decreased in two patients who also had signs of increased air way resistance

6 Alveolar gas exchange was nor mal in all patients.

The liffusion capacity for carbon monoxide was lecreased in eight patients

8 The oxygen transport capacity was limited by circulatory fact rs, due to gravitational shifts of the cen tral blood volume

References

1 Asm ssen, F and M l M Act Phy iol. Scand. 34 1 1954.
2. Astrup P Scand J Clin. & Lab. I st. 8:33, 1956.
3. Barker S. B nd Summerson W J Biol. Chem. 138:535, 1941
4 Bartel H Pflüg. Arch. 254 107 1951
5. Bart ls, H nd Lauë D Pfl g. Arch. 253 126, 1951
6. Bartels, H Burger W Fockweiller H and Lauë D. Pfl g. Arch. 251 127 1951
7 Bart l H nd Rodewald G Pflüg. Arch. 256 113, 1952.
8. Bart l H Böck l E., H rt C. W Rodewald, G nd Schwab M Spri ger Verl g, 1959
9 Becklak M R. Thorax, 7 111, 1952.
10. Berggren S. M Acta Phy iol. scand. 4 ppl. 11, 1942.
11 Bernst l L., D'Silva, J L. and Mend l D Thorax, 7:255, 1952.
12. Bevegård S., Holmgren A nd Jonsson B. Act Phy iol. Scand. 49:279 1960
13. B vegård, S., Holmgre A and Jonsson B Act Physiol. Scand. I preparation, 1961
14. Boothby W M Lundin G nd Helmholt H F Proceed. Soc Exper Biol. 67:558, 1948
15. Carlens E. J. Thoracic S rg. 18 742, 1949
16. Carlens F t Diseases f Chest 36 343 1969
17 Coates E. O and Comro J H J Clin. Invest. 30:848, 1951
18. Dahl trõm, G. Nord. Med 53 417 1955.
19 Daal ls, A C. Diseases f Chest. 16.368, 1949
20 Donevan, R. E., Palm W H Yarvl C. J nd Bates, D V J. Appl. Physiol. 14 483, 1959
21 Ehrner L. and Madl O. Acta Med. Scand. 165:96, 1959



Fig. 11 a. Ca e 8, 28 11 1958. Laten l e partly confl ent mili ry densities i both l ngs.



Fig. 11 b. C 8, 4 7 1960; Since 1958 d rease f the miliary lesions.

13 2)) ECG in upright positi n during and after the work te t showed slight ST and T deviations of the "sympa tieoto nic" type grade 2—3 according to a classificati n reported earlier from thi laboratory (20). In seven patient the ECG was within normal variations

Basal metabolic rate. BMR was on an average + 8.2 (range —9 + 19) % f the predicted n rmal value (20) (Table 2)

Orthostatic test. Three patients (Cases 11 17) showed when stan ling very marked increase in heart rat (120 140 an l 130 beats/min re pect ely nd also fell above twice t l t erro f estimate in the rela een p se rate standing and or f l build (the ratio heig ht) n rmal material repor earlier fr l lab ratory (2a) (t e patient 14 21 3) dem trated a n i ncrease in pulse rate to 106 110 and 100 beats min respectively. Two male and three female patients had only a moderate increase in pulse rate (Tab le 2)

Total amount of hemoglobin was on an average 9.03 (range 8.0—11.52) g kg body weight in the men and 8.66 (range 7.3 —9.97) g kg body weight in the women. Both groups ha l lower values than are ordinarily f und in similar materials (2a). The difference from a value predicted fr m l ody weight was however n t stati tically significant ($p > 0.05$)

Cases 11 14 16 21 27 37 38 also had a low hemoglobin concentration and should be classified as anemic (60)

Blood volumes were on an average 7 ml kg b dy weight (range 0—89) for men, and 75 ml kg (range 68—80) for women. The values fell within the normal variation reported earlier fr m this laboratory (27). Compared with

STUDIES ON THE CARDIOPULMONARY FUNCTION IN SARCOIDOSIS

II

Patients with Parenchymal Infiltrations of the Lungs but without Radiological Signs of Fibrosis

B

NILS SVANBORG

The pure sarcoidotic infiltrate found in the lungs, consists microscopically of epitheloid cells forming noncaseating granulomas. The lesions may remain unchanged, disappear completely or progrediate. The healing process seems to take place via hyalinization or fibrosis (22, 42, 55 64 65). It is thus obvious that the clinical picture and the concomitant functional disorders should vary with the stage of the disease. Pulmonary function in sarcoidosis of the lungs has been studied by a number of investigators (11 13, 14 17 43, 50 51 52, 56, 58 60 62, 67 68, 70). Clinical data presented often do not allow of an adequate definition of the stage of the disease at the time of investigation. The validity of a classification according to the duration of the disease depends on the precision with which the debut of the disease can be established. Since the symptomatology in sarcoidosis is poor the disease is often discovered via routine x ray or at a stage when more pronounced symptoms have appeared.

Studies of the pulmonary function in patients with pulmonary lesions but no obvious signs of lung fibrosis have yielded varying results. In the earliest report of physiologic studies (11) it was demonstrated that a reduction in lung volumes was usually present, an observation that was later confirmed by several authors (1 37 58). In a group of cases with "pulmonary sarcoidosis of recent origin" the most important abnormality was a reduction of all lung volumes, together with mild hyperventilation both at rest and during exercise and an impaired gas exchange in some cases (62). In another material corresponding findings were reported but also in some cases a slightly elevated pulmonary artery pressure (51). Other authors have found an essentially normal cardiopulmonary function (67) except for in some cases, an impairment of the diffusion (50 60 67).

The present report is part of an investigation on the cardiopulmonary function in sarcoidosis. In a preceding paper the findings in cases with

Table 3 Observations during heart catheterization in 11 patients with sarcoidosis

Case no.	Catheterization no.	Work load, kpm/min	Pulse rate beats/min	Oxygen uptake ml/min	Mechanical efficiency per cent	Ventilation l BTPS/min	Ventilation, l (BTPS)/oxygen uptake, l (STPD)	O_2-capacity ml/100 ml	O_2-sat., per cent		AV O_2 diff ml/l	Cardiac output, l/min
									Br A	PA		
12	12/59	Rest	96	239		8 09	33.8	14 7	102	80	36	6.8
		200	127	758	18.6	22.42	29 7	15.3	101	57	70	10.8
		400	148	1151	20.9	31.58	30 0	15 4	102	49	85	13.5
38	11 60	Rest	91	251		6 40	25.5	12.7	98	73	33	7.6
		200	131	767	18.6	18.13	23.6	13.1	98	47	66	11 6
		400	162	1147	21.3	31 04	27 1	13 7	98	43	72	15 9
16	25 59	Rest	78	261		10.83	41.5	18.7	100	80	41	6.4
		200	126	1139	16.3	36 09	31 7	18.9	100	34	79	14 4
		600	150	1732	19.5	66.56	38.4	17 4	100	40	105	16.5
		900	172					18.1	97	21	125	
27	64 59	Rest	72	232		6 28	27.0	15.0	100	61	30	7 7
		200	112	782	17.5	20 03	25 6	15 4	100	59	67	11.8
		400	130	1130	21.3	29 70	26.3	16.0	101	53	79	14.2
23	50 59	Rest	77	336		8.57	25.5	18.3	98	79	37	9.0
		600	126	1584	22.9	39 01	21 6	19.3	98	51	93	17.0
		900	158	2272	22.2	64 31	56 6	20.1	94	44	103	22.1
21	38 59	Rest	74	250		7.34	29.4	15 7	101	75	40	6.2
		200	119	993	19 2	26.77	26.9	16.6	100	55	78	12.7
		600	158	1565	21.8	48 28	30.8	17 2	98	48	88	17 7
11	10 59	Rest	102	246		8 03	32 6	14 0	101	80	32	7.6
		200	126	733	19 7	20.24	27 6	14 1	100	55	66	11 0
		400	152	1065	23.3	30.39	28 5	14 4	99	41	72	14 5
19	35 59	Rest	90	236		7 40	31 4	16 0	99	61	33	7 2
		200	114	770	18 0	21 39	27 8	16 3	100	60	69	11.2
		400	136	1099	22 1	33 33	30.2	16.4	98	49	82	13 4
37	7 60	Rest	87	267		8 02	30 0	14 9	93	71	33	8 0
		100	110	736	10 3	21.32	29 0	13 7	92	56	57	12.9
		200	123	931	14 5	28.70	30.8	15 4	90	49	62	15 0
14	19 59	Rest	91	215		7 00	32 6	14 7	98	79	34	6 4
		200	121	667	20.2	18 65	28 0	15.4	101	58	72	9.2
		400	148	1010	23 2	31 62	30 6	16 6	99	43	87	12 0
5	74 58	Rest	96	378		10 80	28 6	17 8	94	70	44	8 6
		200	122	1113	13 1	29 22	26 3	16 5	96	57	74	15 0
		400	130	1235	20 6	30 84	23 1	19 0	95	49	83	1 8

Br.A brachial rtery PA pulmonary artery PCV pulmonary capillary venous pressure
XL = excess lactat RA right trium

Reason for admittance		Clinical investigations				Time interval from (months)			X-ray fig. no.	Clinical course after examination
Symptoms	X-ray	SR mm hour	Mantoux	Electrophoresis g	Other findings	Last normal lung X-ray	First path. lung X-ray	First symptoms		
—		9	–	Normal		10	2	(2)	1	From April 1959 slow improvement
–		21	–	Normal		36	3	(4)	2	From Feb. 1960 slow improvement
—		8		(α_2 0.7) β 1.0	White blood cells in 11 eos AS 400	105	38		3	Improvement 1960
(+)		19		Normal	AS = 250 Blood pressure 100/70 Serum iron 0.041 mg	16	4	12	4	Increase of parenchymal lesions till August 1959 thereafter slow improvement.
		6		β 0.93	AS 560	48	36		5	1958-1960 Increasing infiltrates (some atelectasis) in part of the right upper lobe
		49		α_2 1.0 β 1.1 γ 2.4	AST = 4.0 AS = 560	41	4		6 a-b	1959-1960 improvement on X-ray but Feb. 1960 hypercalcaemia and tired. July 1960 left nephrectomy showed calcinosis and small hypernephroma.
–		84		$\alpha_2 = 0.8$ $\beta = 1.0$ ($\gamma = 1.6$)	White blood cells in 6.8-3.5 eosinophils slight anaemia AS = 400	29	2	4	7 -b	Aug. 1959-1960 almost fully recovered (cortisone June 1959-Jan. 1960)
		23		$\gamma = 2.0$	AS = 200	13	2		8	Improvement during 1960

titer AST = antistaphylolysin titer

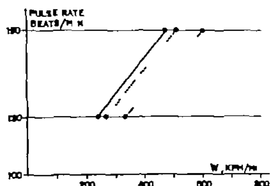


Fig 15. Pulse rate, beats per min. (abscissa) in rel ti n t rat f work, kpm/min. (ordinates) Full li represents exercise in sitti g positi n, dotted line exercise in pine positi d ri g heart catheterizati n and broken li exercise i supine positi n.

(Cases 11 21 23) outside once standard error of estimate

Working capacity in supine position The patients had lower pulse rates when working in supine than in sitting position on the same load and as a rule could not perform work that increased the heart rate to or close to 170 beats/min usually due to pains in the leg muscles Using the approximate linear relationship between rate of work and pulse rate work at pulse 120 and 150 (W_{120} W_{150}) was calculated in each subject (32) Also W supine was calculated by extrapolating from the line between 120 and 150 beats min The value for W_{170} supine calculated in this way was used only for the comparison with W_{170} sitting.

Compari on between work in sitting and supine p itions The difference in heart rat l i work at the same load in both i n irrespective of pulse level (l l l 2 vas found to average 18.31 be i higher in sitting positi n 40) The difference in per cent pulse level in sitting position was on an average 11.5 (range 4 4—23 0) % Both differences were statistically highly significant (p = < 0 001***)

Analysis of the difference between W_{170} and W_{150} in sitting and supine positions (Fig. 15) showed an average of 93.8 kpm/min for W_{150} and for W_{150} an average of 124 4 kpm/min, higher values in supine than in sitting position. Both differences were statistically highly significant (p = < 0 001***) The calculated value for W_{170} supine was on an average 159 kpm/min higher than W_{170} sitting, which difference was also statistically highly significant (p = < 0 001***)

HEMODYNAMIC STUDIES

Right heart catheterization was performed in all patients without complications except for a transient right bundle branch block in one patient

Hemodynamic data obtained in connection with the heart catheterization are presented in Table 3

The pulse rate at rest was 83 4 (range 74—102) for the males and 87.8 (range ›2—96) for females

The oxygen uptake at rest was higher than the predicted basal value 21.3 (range 10.3—33.6) for the males and 25 4 (range 10 4—39 1) % for the females, or significantly higher than the BMR.

During exercise the oxygen uptake increased with increasing working intensity corresponding to a mechanical efficiency of 20.9 (range 14.5—23.3) % on the highest work load

Reason for admittance		Clinical investigations				Time interval from (months)			X-ray Group fig. no	Clinical course after examination
Symptoms	X ray	SR mm/hour	Mantoux	Electrophoresis g%	Other findings	Last normal lung X ray	First path lung X ray	First symptom		
		48	+	$\gamma = 2.5$	Serumcalcium = 11.2 mg % AST = 2.8	36	1	9	9 b	X-ray unchanged or slowly deteriorating 1960
	+	22	(+)	Normal	—		31	40	10	During 1960 increasing but then decreasing parenchymal densities (cortison from April 1959)
		17	+	$\gamma = 2.3$	Right leg 4 cm shorter than left	36	1	7	11 b	X-ray unchanged 1959 improvement 1960.

Blood vol. l	Blood vol. ml/kg	Pulse rate standing, beats/min	W_{170} sitting, kpm/min	Highest load in sitting position				Orthostatic test Pulse rate after work		
				kpm/min	Duration min	Pulse rate beats/min	Respiratory breath/min	Load, kpm/min	Sitting, beats/min	Supine beats/min
4.7	79.7	120	375	500	4	184	30	400	174	134
4.4	76.8	110	460	600	4	182	25	600	161	154
5.0	89.2	80	900	900	8	170	34	600	142	124
5.5	77.5	82	690	800	4	177	34	600	160	146
6.0	70.6	92	1100	1200	6	176	40	900	153	152
4.7	71.2	110	640	900	6	200	35	600	164	146
3.1	82.3	140	480	600	4	185	30	400	162	142
4.4	75.9	110	800	600	8	169	31	600	169	152
4.6	67.7	106	650	800	2	160	54	200	116	106
4.0	74.1	106	500	600	6	177	40	400	157	128
6.5	69.9	120	600	600	6	168	28	400	165	120
5.46 4.7–6.3	76.63 69.9–89.2	104.4 80–140	744.0 480–1100	840 600–1200	5.6 4–8	179.8 168–200	33.2 28–40	550 400–900	157.6 142–165	128.8 124–152
4.58 4.0–5.3	75.25 67.7–79.2	107.2 82–130	545.8 375–690	617 500–800	4.3 2–6	174.8 160–184	35.7 25–54	467 200–600	156.2 116–174	130.2 106–154

globin W_{170} = working intensity at pulse rate of 170 beats/min.

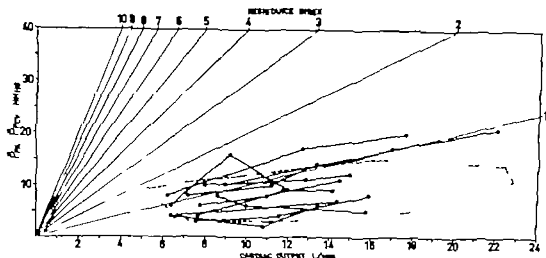


Fig 16 Press re gradient ove p lm ry vasc l bed, pressed th difference between pulmo ry ar erial mea pressure ($\overline{P}_{PA}$) nd pulm ry pill ry ven pres re ($\overline{P}_{PCV}$) i mm Hg (rdi t) i relati t rdi tp t, l/min, t rest d d ing exercise. *H tched rea represe t the n rmal ra g fou d in thi laborat ry (30)* The bliqu ll es re isoresi tance i dex ll es.

working intensity The relationship between brachial arterial pressure (y) and pulse rate (x) is expressed by the regression equation y = 74 7 + 0 198 x. *This regression does not sig* nificantly differ from the normal equation (30) As mentioned above Case 21 who had an overall pressure increase during work, had an arterial mean pressure rise to 165 mm Hg during heavy work.

Oxygen saturation of the arterial blood was on an average at rest 98.5 (range 93– 102) %. During work it decreased slightly but not significant ly to 97.3 (range 90—102) % Simul taneously the O *capacity* of arterial blood increased on an average 0 98 vol % (1.26 for the males, 0 75 for *the females)* All values *fell* within the normal v ri ti ns (24 30) except in patient 37 h also at the study of ventilation n l bl l gases at rest and during exercise in sitting position had low values for P_{aO_2} and a high venous admixture (Table 3)

Mixed venous oxygen saturation $S_{\bar{v}O_2}$ *varied between 70—81 % at rest* (Fig 17) During exercise it decreased with increasing working intensity and heart rate The lowest values in each individual varied between 31 and 53 %. At rest two patients (Cases 11 12) had a slight tachycardia and slightly high values but at work the relation ship between $S_{\bar{v}O_2}$ and heart rate was normal in all cases (, 30)

Arterio-venous oxygen difference (AVD) ml/l at rest varied between 30 and 44 ml/l *i.e* within the limits of the normal variation reported earlier from this laboratory (7 25 30) Muscular *work increased AVD with increasing* working intensity oxygen uptake and pulse rate to maximal values between 62 and 125 ml/l Plotted again t $\dot{V}_{O_2}$




Fig 5 C 23, 10 8 1939 Right paratracheal nd BHL. Some mill ry densities i both l ngs. Coalescent den ities with some t lact sl ce trally in the right l g.

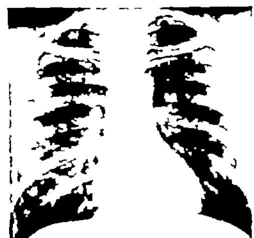


Fig. 6 a. C 21 27/8 1939 Moderat mili-ary nd some odular densities in both l ngs.



Fig 6 b C 21 11/4 1940 Decrease of p renchym l densities since 1939 Now few linea densities.

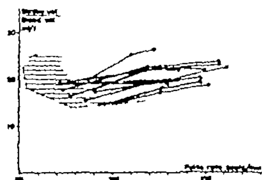


Fig 21 Stroke volume divided by blood volume, ml/l, in relation to pulse rate beats/min, at rest and during work. Symbols as in fig 17

males and 12.0—15.9 l/min for the females. The increase in relation to increasing $\dot{V}_{O_2}$ lies within normal limits (7, 30) in all patients but *one* (Case 37) who had a higher value than normal the greatest load (Fig 20)

Stroke volume at rest varied between 76 and 117 ml for the males and 69 and 107 ml for the females.

The stroke volume during resting conditions amounted for the men on an average to 1.68 % of the blood volume (range 1.40—1.95) and to 11.9 % of the heart volume (range 9.71—13.33) or significantly lower than reported in a normal material. Corresponding values for the females were 1.82 % of blood volume (range 1.47—2.0) and 12.43 % of heart volume (range 10.61—15.23) or slightly lower than reported normal values (7, 30)

On the transition from rest to work there was a significant increase in stroke volume ($p < 0.01$**) of 21.8 ml (range + 12 — + 32) or 24.3 % of the resting value in the male group. The female group showed a probably significant increase ($p < 0.05$) with 11.5 ml (range — 2 — + 25) or 14.6 % of the resting value. *During continued work with increasing load there was a further increase of stroke volume in all patients except Cases 5 and 10 who showed a small decrease of 2 and 1 ml respectively. The difference between stroke volume obtained at rest and at the highest work load was highly significant for the males ($p < 0.001$***) and significant for the females ($p < 0.01$**)*

The relationship between heart rate *and stroke volume/blood volume* varied within the normal range both at rest and during work, except that five *patients (Cases 11, 14, 19, 37, 38)* had a slight tachycardia at rest (Fig 21)

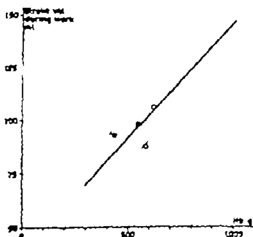


Fig 22 Mean values for all observations of stroke volume during work in each subject, ml, in relation to total amount of hemoglobin, g. Straight lines indicate normal regression between these parameters (Holmgren *et al.* 1960) ± standard error of estimate



Fig 9 a. C 37 27 1 1960 M rk d mil ry nod la nd coalescent pat hy den ities both l ngs.



Fig 9 b C 37 8 9 1960 Duri g 1960 I rease f nod la nd coalescent pat hy den ities I both l gs.

fossa supraclavicularis (15) or media linum (12) Gastric lavage tests on guinea pigs, microscopic examina tions or culture n lymph node ma terial were negative f r tuberculosis. All patients were ho pitalized for at least two weeks, during which time the study was perf rmed The plan of investigation and the methods em ployed have been reported earlier (32)

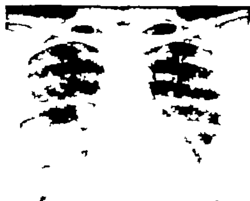


Fig 10 C 14 10/12 1958 M rked mili *ry nd nod la densities in both l gs.* Some pleural inv l ement.

Results

Electrocardiograms ECG was within the normal variation at rest in ten patients One patient (Case 19) show ed a slight deviation of ST and T at rest this deviation was accentuated in upright position During work, the ECG in this patient showed transient ventricular extra systolles but de- crease of ST and T-deviations No signs of myocardial insufficiency or valvular lesions could be demonstra ted heart volume, stroke volume, ar terial and intracardiac pressures were normal In three patients (Cases 12,

Table 4 Lung volumes l BTPS oxygen uptake of each lung in per cent of total nitro-

Case no.	IRV	TV	ERV	VC		FRC		RV	
				Obs., l	% of pred.	Obs. l	% of pred.	Obs., l	% f pred
12	1.59	0.31	1 40	3.30	76	2.81	90	1.22	73
38	1 11	0 44	0.85	2.30	62	2.30	97	1 66	131
16	2.50	0.6.	1 93	5 10	92	3 11	74	1 12	57
27	1.81	0 66	1 49	3.86	91	2.28	92	1.02	72
23	2.34	0.65	0 80	3.79	69	1.32	51	0.85	38
21	2 66	0.54	1 40	4 60	88	2.71	64	1.31	56
11	2.35	0 63	1 92	4 90	90	3.65	90	1 73	92
19	1 72	0 67	1 28	3.67	106	2.37	103	1 15	87
37	1 03	0.56	1 40	.99	82	3.34	119	1.96	106
14	1.67	0.32	1 04	3 03	93	1 74	78	0.77	59
5	1 67	0.67	1 13	3.47	60	2.34	60	1 06	58
♂ M	2.304	0.628	1 440	4.372	80	2.618	70	1 222	64
Range	1.67 3 66	0.54—0 67	0 80—1 93	3.47—5.10	60—92	1.52—3.65	61 90	0.85—1 3	56 92
♀ M	1 488	0 493	1.227	3 192	66	2.473	97	1.300	90
Range	1 03—1.81	0.31—0 67	0 85— 1 40	2.30 —3 88	62 106	1 74 3.34	78 119	0 77 1 96	59 131

IRV = inspiratory reserve volume TV = tidal olume ERV expiratory reserve olume VC = ital capacity nitrogen wash-out index.

observed — predicted value for the group was statistically significant ($p < 0.01$**)

The total lung capacity was 5 00 litre or 81 % of the predicted value (range 60—90 % for the males and 76—100 % for the females) In four males (Cases 5, 16 21 23,) and one female (Case 12) the value was lower than twice SD from the predicted normal value (23) The difference between *observed and predicted value* for the group was statistically highly significant ($p < 0.001$***)

The qu tient RV x 100 TC wa 25 4 or somewh t lower than the predicted value r nge f r the males 67—100 and f r the females 74 167 %) In tw n l C ses 16 21 the value was lower in one female (Case 38) higher than twice SD from predicted normal value (23) The difference for the group ($p < 0.6$) was not significant however

Ventilation gas exchange diffusion blood gas tensions and anatomical blood shunt values for lactic and pyruvic acids were studied at rest in supine and during work in sitting position (Table 5)

With an average work load of 482 (range 300—900) kpm/min, heart rate increased to 148.5 (range 130—177) beats/min Respiratory rate increased to 23 6 breaths/min, $\dot{V}_{O_2}$ increased to 1431 (range 896—2347) ml/min, corresponding to a mechanical efficiency f 10 4 (range 14.8—21.) a slight

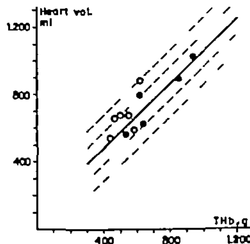


Fig 12 H rt ol me, ml, (ordinat) i rela tion t tot l mou t f hemoglobl (bscis-) Filled circles represent males d pen circles females. Straight line represent or mal regres ion line, described by Holm gre et l 1937 (23) Broken lines indicat ± st nd rd error f estim t nd twice t ndard error f estim t

a value predicted from body weight it was slightly higher than nor mal statistically probably ignificant ($p = < 0.02$)

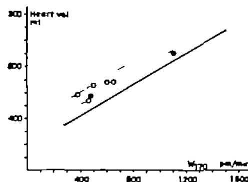


Fig. 13. H rt ol me, ml, (ordi t) i re- lation t rat of work t pulse rat of 170 beats/min. (W_{170}) kpm/min, (bsci sa) Symbols as in Fig. 12.

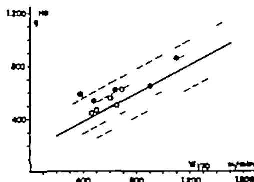


Fig 14 Tot l amou t of hemoglobin, g (ordi nat) i relation t W_{170} kpm min. (abscis- sa) Filled ymbols represent males nd open mbol fem les. Norm l regres ion li i Fig. 12.

The heart volum in prone position was normal in relation to THB (Table 2 Fig. 12) *i.e* within twice standard error of estimate in all patients (25) There was no statistically significant difference from a value predicted from THb ($p = > 0.1$)

Working capacity sitting (W sitting) (39 66) In Case 37 the high est work load could be performed for only two minutes with a pulse rate of 160 beats min. The other ten patient could perform work that increased the heart rate close to or over 170 beats/ min (Table 2)

In ten patients W_{170} lay to the left of the regression line in the relation W_{170} to heart volume (Fig 13) In three patients (Cases 5 21 27) W_{170} fell outside twice standard error of estimate and in five more (Cases 11 12, 14 19 37) outside once standard error of estimate Relation W_{170} and THb behaved in a similar way (Fig 14) in two cases (Cases 5, 12) W_{170} fell outside twice and in three patients

Table 5 Alveolar ventilation diffusing capacity and related values in patients with

Case no.	Work load, kpm/min.	Pulse rate beats/min	Respiratory rate breaths/min	$\dot{V}_E$ l BTPS/min	V_T, ml BTPS	$\dot{V}_{O_2}$ ml STPD/min	$\frac{\dot{V}_E \text{ l BTPS}}{\dot{V}_{O_2} \text{ l STPD}}$	RQ	Mechanical efficiency per cent	V_D, ml BTPS	$\frac{V_D}{V_T}$	Pa_{CO_2} mm Hg
12	Rest 300	80 141	19 24	7.89 30 48	0.42 1.27	225 995	35 1 30 6	0.82 0.93	18.5	134 151	0.32 0.12	33 32
33	Rest 400	84 152	16 18	6.93 28.43	0 43 1.58	199 1137	34.8 25.0	0.83 0.90	20 4	159	0.37	38 31
16	Rest 600	54 124	23 19	11.32 48.86	0.49 2.57	237 1637	47.8 29.8	0 98 1.03	20.5	201 289	0.41 0 10	35 31
27	Rest 600	80 164	12 23	6.81 48 63	0.57 2 11	202 1664	33 7 29.2	0 96 1.03	19 6	119 45	0.21 0.02	34 32
23	Rest 900	76 150	14 24	8 99 64.37	0.64 2.88	347 2347	25 9 27 4	0.70 0 89	21.5	172 416	0.27 0 16	33 34
21	Rest 500	72 141	12 17	8.25 37.23	0 69 2.19	262 1423	31.5 26.2	0.82 0 92	20 6	215	0.31	38 31
11	Rest 400	90 177	18 24	10 66 37 97	0.58 1.58	278 1275	38 4 29 8	0 81 0.83	18 1	206 514	0.37 0 33	34 37
19	Rest 400	86 149	17 23	8.20 32 62	0 48 1 42	218 1152	37 6 28 3	0.81 0.83	20.4	182 272	0.38 0 19	33 33
37	Rest 400	66 137	12 34	7.36 46.18	0.61 1.36	232 1260	31 7 36.7	0 79 0 93	18.5	181 395	0 30 0.29	34 33
14	Rest 400	72 146	20 28	7.08 32.82	0.35 1 17	206 1181	34 4 27 8	0.81 0 93	19.6	88 148	0 24 0 12	34 35
5	Rest 400	76 140	17 26	11.56 43.16	0.68 1 74	375 1664	30.8 27 1	0 69 0 92	14.8	234 360	0 35 0 21	35 34
Rest M Range		74.2 54 90	16.4 12 23	8.386 6.81 11.56	0 530 0.35- 0.69	252 7 199 375	34 3 25 9 47.8	0.82 0 69 0.98		17 1 75 239	0 327 0 21 0 41	35 0 31 38
Work M Range	482 300 900	148.5 136 177	23.6 19 34	41 158 28 43 64.37	1 789 1 1 2.88	1430.5 995— 2347	28 90 25.0 36.7	0 92 0 82 1.03	19 41 14 8 21.5	283.6 45 514	0 172 0 02 0 33	33 3 31 37

Symbols and abbreviations according to Pappenheimer et al Federation Proc 1950 9 602 XL excess lactate

38) the physiological dead space value decreased or could not be determined, probably because the patients were not in a respiratory steady state during the study

The relationship between dead space and tidal ventilation (V_D/V_T) was in all cases normal at rest or on an average 0.327 (range 0.21—0 41) and decreased during exercise to 0 172

ung infiltrates.

Strok. vol ml	Lactic acid, mE/l	Pyruvic acid, mE/l	XL mE/l	Pressures, mm Hg										Palm. vasc. resist. index.
				RA	RV		PA			PCV	BA			
				M	S	De	S	D	M	M	S	D	M	
69	0.61	0.09		6			21	14	18	14	117	68	85	1.01
85	1.61						26	16	19	17	125	62	86	0.40
91	2.82	0.203	1.26				30	19	24	18	133	70	92	0.76
83	1.29	0.115		0.5	18	2	14	4	10	6	113	64	82	0.63
88	2.17				33	4	25	13	22	17	128	69	100	0.54
95	3.95	0.223	1.33		34	2	25	13	21	13	142	69	100	0.80
82	1.17	0.110		3	23	5	25	8	15	9	122	62	80	1.08
114	3.05				47	3	39	14	22	15	143	86	91	0.92
110	4.53	0.280	1.59		51	5	43	14	23		147	73	97	
	8.83	0.390	4.69		83	3	36	18	23	13	154	77	100	
107	0.72	0.063		0	19	6	19	7	14	10	103	59	78	0.93
103	1.65				28	5	28	12	21	15	122	63	85	1.39
109	2.89	0.185	0.81		33	2	29	14	19	15	137	62	93	1.15
117	1.00	0.075		1	26	6	23	9	13	4	107	60	79	2.23
133	—				48	0	34	12	23	6	138	64	90	2.00
140	5.85	0.280	2.15		33	−1	36	13	22	7	147	74	98	1.90
84	0.89	0.060		1.5	22	4	23	7	13	6	131	79	106	2.39
107	1.89				47	7	41	16	25	16	178	83	122	2.48
112	4.03	0.220	0.79		59	8	47	19	31	20	215	100	153	2.09
78	0.94	0.093		0	19	4	17	8	11	4	126	78	94	1.36
88	1.50				29	3	26	9	14	8	142	82	104	1.29
96	1.83	0.165	0.19		40	5	35	8	18	7	154	78	102	1.34
79	1.11	0.075		1	26	3	17	3	10	5	128	70	94	1.76
97	1.83				43	11	32	13	19	14	158	82	106	1.41
99	3.23	0.195	0.44		47	10	35	14	23	12	164	76	106	1.65
92	1.06	0.093		0	27	3	22	4	16	6	113	68	87	2.27
117	1.00						33	15	24	13	137	75	97	1.55
122	1.33	0.130	0.11				31	15	24	12	138	72	97	1.46
70	1.23	0.063		1	20	3	17	10	13	5	108	75	92	1.43
77	1.01				37	3	25	14	20	7	123	77	97	2.64
81	2.44	0.173	0.14		42	2	33	14	22	7	136	81	102	1.14
100	1.06	0.033			19	−1	19	5	12	2	112	65	81	2.03
124	1.65				30	0	30	12	20	15	144	81	105	0.87
122	1.83	0.003	±0		31	−3	29	6	19	11	143	80	100	0.69

S = systolic D = diastolic De = end diastolic M = mean Palm. vasc. resist. index = $\frac{\bar{P}_{PA}-\bar{P}_{PCV}}{Q_i m^2_{bs}}$

was 9 / mm Hg (range 59—108) The mean value was lower than that in a normal material reported earlier from this laboratory (26) Three patients (Cases 5 11 37) had values lower than twice SD of this normal material During exercise the P_{aO_2} increased to 82.5 mm Hg (Range 64—92) which is still within normal limits in all patients but one (Case 37)

The arterial carbon dioxide tension at rest was 35 0 mm Hg (Range 34—38) or within normal limits. During exercise it decreased to 33.3 mm Hg (range 31—37) which is within the normal range (26)

The arterial pH at rest varied between 7.360—7 439 (mean = 7 409) In one patient (Case 37) the pH lay below twice SD in the variation reported earlier Standard bicarbonate was slightly low and lactic acid concentration high in this patient. During exercise it varied between 7.322 and 7 411 (mean = 7.384) or within the limits for the above mentioned normal material.

Standard bicarbonate at rest varied between 19 0 and 23.0 mE l or slightly below normal in one patient (Case 3) During exercise it varied between 18 0 and 21 0 or slightly below normal in Case 14 (26)

Lactate and pyruvate concentrations f arterial blood were determined at rest and during the exercise test in ventilatory studies (Table 5) Lactate concentration at rest was on an average 1.322 mE l, a normal value (range 0.94—2 00) One patient (Case 37) had a somewhat high value (2. 28)

During exercise 11 d lactate increased to 3.953 (range 1.89—5 72) mE l, all values being within the normal range

During exercise the excess lactate (33) which indicates the amount of anaerobic work performed, averaged 1 42 mE l (Range 0 40—2.80)

Venous admixture to arterial blood in the lungs due to an anatomical shunt was found to be significantly (3 4 6 57) high in three patients (Cases 11 27 37) or 7 7 6.0 and 16 0 % respectively and slightly high in three other patients (Cases 12, 14 19)

Distribution of inspired gas (Table 4) N wash-out time was on an average 2.87 min (range 1.6—4) Only one patient (Case 37) showed a value higher than normal two (Cases 10 21) were border line cases (9 44)

The volume ventilated during N wash-out time per litre FRC, *i.e* the wash-out index (5) averaged 9 01 (range 6.3—11.8) Two patients (Cases 11 37) showed values higher than twice SD above normal value two (Cases 16 19) were borderline cases

Broncho-spirometry (Table 4) showed that the right lung had, on an average 50 7 % of total oxygen uptake (range 37—66)

Two patients had values differing from the normal variations (8 63) Of total oxygen uptake Case 5 had only 34 % on left lung and Case 23 only 37 % on the right lung. Case 5 had extensive densities in both lungs. Case 23 had a long standing atelectasis of the right middle lobe and small infiltrates in the other parts of the lung fields

(200—900 kpm min) increasing the pulse rate to 143 beats min (range 123—172) (66 71 72)

Pulse rate at work was somewhat higher during heart catheterization than otherwise during exercise in supine position (Fig. 15)

Right ventricular pressures varied within the normal limits. The systolic pressure was on an average 21 9 mm Hg at rest (range 18—26) The end diastolic pressure was 3.5 mm Hg at rest (range —1 + 6) During exercise the systolic pressure increased to 43.6 (range 31— 9) the end-diastolic remained unchanged or increased slightly (Cases 19 21)

Pulmonary arterial pressure Systolic pressure at rest was 19 7 mm Hg (range 14—25) Corresponding figures for mean and diastolic pressure were 13.4 (range 10—18) and 7 (range 3—14) mm Hg respectively The mean pressure during exercise can be expressed by the regression equation $y = 14.8 + 0.048\ x$ where y is mean pressure in the pulmonary artery in mm Hg, and x is heart rate beats/min. This regression is not significantly different from that found earlier in a normal material (30) However in one patient (Case 21) with increasing pressures during work (600 kpm min) also in the RV and the brachial artery the pulmonary systolic pressure rose to 47 mm Hg and mean pressure to 25 and 31 mm Hg. No signs of valvular lesions or myocardial insufficiency could be demonstrated, heart size and stroke volume were normal as well as ECG at rest and during exercise

During work a pressure gradient across the pulmonary valve up to 17 mm Hg (Cases 16, 23) could be observed, values often found in a normal material (30)

PCV pressure at rest was 6.5 mm Hg (range 2—14) The pressure-changes with increase in pulse rate during exercise can be expressed by the equation $y = 14.8 - 0.016\ x$ where y is mean wedge pressure in mm Hg and x is heart rate in beats/min The mean pressure during exercise was 12.3 mm Hg (range 7—20) From rest to heavy exercise individual increases of 0 (Case 5) and 10—14 mm Hg (uncertain value Case 21) were observed No signs of valvular lesions or myocardial insufficiency could be demonstrated in those cases.

The pulmonary vascular resistance index expressed as $(\bar{P}_{PA} - \bar{P}_{PCV})/Q$ m² BSA was normal at rest = 1.56 (range 0 63—2.30) units in all patients.

During exercise the resistance decreased to an average of 1.30 (range 0.69—2 09) (Table 3) Four patients had values on the border to or slightly above normal limits (Fig. 16)

Right atrial pressure at rest was recorded normal in ten patients = 0 (range —1 + 6) and was omitted in one patient.

Brachial arterial pressure at rest was on an average Systolic 116 4 (range 103—131) mm Hg. Diastolic 68.3 (range 59—79) mm Hg. Mean pressure 87.3 (range 78—106) mm Hg Thus the arterial blood pressure at rest was well within the range of the normal variation. During exercise the pressure rose with increasing

Table 6 Mechanics of breathing in 11 patients with sarcoidotic lung infiltrates.

Case no	MVV free			MVV$_{40}$		MVV l/min	MVV l/min	FVC		FEV$_1$	
	Obs. l/min.	% of pred.	Rate	Obs. l/min.	% of pred.			Obs. l	% of pred.	Obs. l	% of pred.
12	82	64	50	62	58	76	78	3.80	91	3 41	100
38	77	83	65	47	44	60	71	2.85	80	2.46	74
16	153	81	52	89	57	97	118	5.01	96	4 41	99
27	92	74	68	67	62	97	98	4 11	103	3.58	107
23	122	85	61	105	69	130		3.95	78	2.89	68
21	175	111	76	133	104	153	164	4 63	101	3.62	99
11	116	62	44	114	73	136		4.08	92	2.89	66
19	61	54	48	60	61	100	66	3.63	110	2.60	84
37	67	65	52	57	70	63	58	3.12	91	2 14	84
14	70	63	64	36	38	48	61	3 11	101	2.45	82
5	177	103	80	94	68	120	139	3.59	72	3.34	83
♂ M	148.6	84	63.3	107 0	75	129 4	140.3	4 446	88	3.430	83
Range	116 177	62 111	52—80	89 133	37 104	97 153	118 164	3.59 5 01	72 101	2.89 4 41	66 99
♀ M	74.8	64	53.0	54.8	65	73.8	72.0	3.435	96	2 773	80
Range	61 92	54 74	48—68	36 67	38 70	48 100	58—98	2.85—4 11	80 110	2.14 3.58	74 107

Maximum voluntary ventilation = MVV free MVV breaths/min. Forced vital capacity = FVC, forced flow = MMF maximum midinspiratory flow = MMIF forced inspiratory volume in one second = FEV

twice standard deviation three more patients (cases 16 27 37) lower than once SD from the predicted normal value The difference between observed and predicted values (3o) was highly significant ($p < 0.001$***) for the whole group MVV$_{40}$ was on an average *78.5 (range 36—133) l/min*, of 64 % of the predicted value (range 38—104) Two males (Cases 16 23) and five females (Cases 12, 14 19 27 38) had values below twice standard deviation from the predicted normal value The difference from predicted value was highly significant for the whole group ($p < 0.001$ **) (3o)

MVV$_{40}$ averaged 99 1 (range 48—153) l min and the corresponding values for MVV$_{40}$ were 94 8 (range 58—164) l/min.

Maximum inspiratory and expiratory flow rates values, see Table 6

Forced Expiratory Volume in one second (FEV) was, on an average 3 072 l sec (range 2 14—4 41) or 86 % *of the predicted value (range 66—107)* (3o) Two men (Cases 11 23) and one female *(Case 38) had values below twice standard deviation from* predicted normal value three females (Cases 14 19 37) had values lower than once SD

The difference from the predicted value for the group was probably significant ($p < 0.02$*)

Forced Expiratory Volume in one

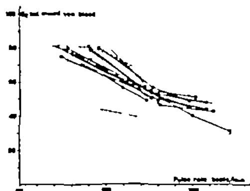


Fig. 17 O ygen sat ration f mi ed enou blood, per cent, relation t pulse rat be t blood, per cent, l rel tion t pulse rat beat ra ge (H lmgre *t al* 1960) is indic ted by broken lines. H tched rea represent resting l es. Filled circles represent males nd open circles females.

(Fig. 18) AVD varied within the n r mal limits. In relation to heart rate two patients (Cases 11 38) had a low AVD on the highest load (Fig 19)

Cardiac output at rest varied be tween 6.2 and 9.0 l min for the males and 6 4—8 0 l min for the females. The corresponding cardiac indices

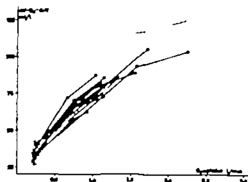


Fig. 18 Arterio-venous xygen difference ml/l in relation t oxygen ptake l STPD min. t rest nd duri g work. Symbols as i Fig. 17

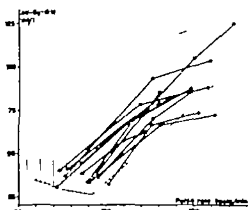


Fig 19 Arterio- nous ygen d fference ml l l relation t pulse rat be t 'min. t rest nd d ring work. Symbol in Fig. 17

were 3.31—4.51 l min m² BSA for the males and 3.88—4 6 l min m BSA for the females

During exercise the cardiac output increased to 14.5—22.1 l min for the

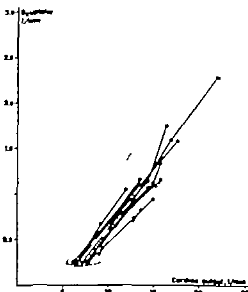


Fig 20 Oxygen uptake l STPD/min. i relation t cardiac output l/min. t rest nd during work. Symbols as i Fig. 17

tients (Cases 23, 37) showed values slightly below reported normal limits (19).

The difference between FIV % and FEV % was statistically significant ($p < 0.01^{**}$).

Compliance Table 6, during resting ventilation averaged 0.109 (range 0.073—0.142) l/cm H_2O or in % of a value predicted from height (19) 57.9 (range 28—88) %. Compliance was also compared with a value predicted from observed vital capacity and averaged 62.5 (range 49—102) % of the predicted value (19).

Three males (Cases 5, 21, 23) and two females (Cases 12, 37) showed values below twice SD from the value predicted from height, four more patients (Cases 11, 16, 27, 38) had values below once SD. The difference from predicted value was statistically highly significant for the group ($p < 0.001^{***}$).

Three males (Cases 11, 16, 23) had values below twice SD from the value predicted from observed vital capacity and three more patients had values lower than once SD (Cases 5, 21, 27). The difference between the observed value and the value predicted from vital capacity was statistically highly significant for the group ($p < 0.001^{**}$).

Total lung Resistance Table 6, during resting ventilation was on an average 2.42 (range 1.25—4.05) cm H_2O/l/sec. Two patients (Cases 23, 3) had values higher than twice SD in a normal material (18, 1).

Compliance and Resistance during hyperventilation (Is mean ± once SD). During spontaneous breathing the tidal volume was 0.684 ± 0.246 l, with a rate of 21.9 ± 4.2 breaths per minute and a pressure variation of 6.476 ± 2.26 cm H_2O.

During hyperventilation the tidal volume was 1.017 ± 0.304 litre at a rate of 23.6 ± 6.7 breaths per minute and a pressure variation of 8.930 ± 3.78 cm H_2O. The relation between compliance at resting ventilation and at hyperventilation averaged 0.93 (range 0.53—1.35). Two patients (Cases 12, 38) had values lower than those reported in normals (19). The difference between the two observed values was statistically insignificant ($p > 0.2$) for the group however.

The relation between the resistance at spontaneous breathing and at hyperventilation was 1.23 (range 0.72—2.33) on an average. Two patients (Cases 12, 38) had values higher than those reported in normals (19). The difference between the two observed values however was statistically insignificant for the group ($p > 0.3$).

Resistance during hyperventilation During hyperventilation and spontaneous breathing the same two patients had resistance values higher than normals. All values fell within twice SD in the correlation reported for normals and patients between R and 1FEV (19).

Discussion

The material (Table 1) consisted of five men and six women with sarcoidotic lung lesions of different degrees, but without signs of fibrosi

To diminish the random variation of the stroke volume due to biological variation a mean value for the stroke volume during exercise was calculated in each individual (30) Plotting this mean value against THI in each case showed that eight patients fell within once standard error of estimate for the normal material Ten patients within twice and only one patient fell outside twice standard error of estimate This patient (Case 3) had a large stroke volume in relation to the THb None had a significantly low stroke volume during exercise (Fig. 22) but two patients showed a slightly low value (Cases 5 12)

In relation to heart volume stroke volume during exercise in five patients

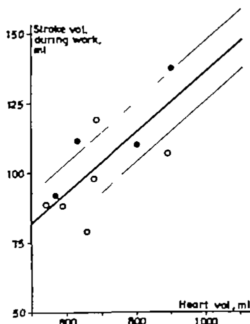


Fig. 23. Stroke ol me, ml, determined I Fig. 22 in relation t heart volume ml. Straight lines indic t normal regres ion between these parameters (30) ± standard error f estimate.

fell within once and in all patients within twice standard error of estimate (Fig 23)

PULMONARY FUNCTION

Static lung volume (Table 4) The results of the determination of the lung volumes are presented in Table 4 *Inspiratory reserve volume* was on an average 1.88 (range 1.03—2.60) litre *Tidal volume* was on an average 0.534 (range 0.31—0.6) litre *Expiratory reserve volume* was on an average 1.324 (range 0.80—1.95) litre

The vital capacity was on an average 3 5 litre or 83 % of predicted value (range 60—92 for the males and 62—106 % for the females) In two males (Cases 23) and two females (Cases 12, 38) the values were lower than two standard deviations from the predicted normal value (23) The difference from predicted value was for the group statistically significant ($p < 0.01$**)

The functional residual capacity was on an average 2.55 litre or 85 of predicted value (range 51—90 % for the males and 78—119 % for the females) In two males (Cases 21 23) the values were lower than two SD from predicted normal value (23) The difference observed — predicted value for the group was statistically probably significant ($p < 0.02$)

The residual volume was on an average 1.27 litre or 77 % of predicted value (range 56—92 % for the males and 59—131 % for the females) In three males (Cases 5 16 21) the values were lower than twice SD from predicted (23) value The difference

pulse reaction in standing position, and at work sitting as compared with exercise in recumbent position (Table 2). This orthostatic reaction, which is not found to the same degree in normal cases (7, 30, 31), may possibly be a sign of abnormal blood volume distribution which may possibly also explain the reduction of W [illegible] sitting.

The increase in stroke volume with change from rest to work in recumbent position may perhaps be explained by the redistribution of peripherally distributed blood. It should be observed that the two patients with marked orthostatism (Cases 5 and 12) had, also during work, rather low but not significantly reduced stroke volumes.

In no case did the low W [illegible] sitting correspond to low cardiac output in relation to oxygen uptake, nor to the increase of pressure in the right ventricle, the pulmonary artery or the PCV; the peripheral adaptation was normal judged as AVD or oxygen saturation in pulmonary blood during work. The pulmonary vascular resistance varied within the limits of a normal material, but if the difference in pressure $\bar{P}_{PA} - \bar{P}_{PCV}$ at rest and during work is correlated to the cardiac output (Fig. 10), four patients (Cases 14, 10, 21 and 23) had values which were either marginal values or somewhat higher than normal range.

Sarcoidosis of the heart is not an un[illegible] finding at post mortem exa[illegible] (34, 42) but the clinical find[illegible] [illegible] sarcoidosis vary [illegible] In a collected aut[illegible] of [illegible] cases with heart sarc[illegible] were thirteen without cardiac symptoms; nevertheless, six of these thirteen had widespread myocardial changes (34). The remaining twenty seven had varying signs and symptoms: seven had died suddenly, ten had cardiac insufficiency, the others, among whom a prominent role was played by disturbances of the atrioventricular bundle, had varying cardiac symptoms. A normal ECG is not, of course, synonymous with the absence of sarcoid involvement of the heart, but in none of the patients in this group were there signs of cardiac insufficiency, AV block or arrhythmia. One patient (Case 19) had premature beats at the beginning of exercise and slight ST T-deviations but no signs of myocardial insufficiency. In three other patients (Cases 12, 14 and 2[illegible]) there were slight ST and T-deviations of the sympatocotonic type but the hemodynamic studies showed normal values.

The results of the hemodynamic study suggest that the displacement of the blood volume in upright position may be a factor limiting the capacity for work in cases of pulmonary sarcoidosis of this type.

Alveolar ventilation judged as P_{O_2} and P_{CO_2} at rest and during work was normal in eight cases. One patient (Case [illegible]) had a reduced P_{O_2} at rest which was normalized during work, one (Case 17) had a rather low P_{O_2} both at rest and at work, one patient (Case 11) had a slightly reduced P_{O_2} at rest, which remained unaltered during work, however. The P_{O_2} values in these cases were normal at rest and during work (as were the stand and bicarbonate values), which in

gen wash-out time N₂ wash out index in patients with sarcoidotic lung infiltrates

TC		$\frac{RV}{TC}$ 100		N_2 wash out time min	$\frac{V\ (F \quad = 2\ )}{FRC}$	O_2 uptake of total	
Obs 1	% of pred.	Obs.	of pred.			Right lung	Left lung
4.32	76	27	104	2.0	8.2	31	49
4.06	82	40	167	1 9	6 4	50	50
6 22	82	18	67	2.5	10 4	33	47
4.88	89	21	81	2.7	6.2	31	49
4.81	66	18	82	1.6	9 5	37	63
3 91	78	22	71	3 7	8.2	50	50
6 63	90	26	100	2.0	11 1	49	51
4 83	100	24	89	3.9	10 4	60	30
4 97	86	29	115	4 7	11.8	60	50
3.80	82	20	74	1 7	7.8		
4.33	60	24	96	2.9	9 0	66	34
3.394	75	21 6	83	2 74	9 64	51 0	49 0
4.33 6.63	60 90	18 26	67—100	1.6—3 7	8.2 11 1	37—66	34—63
4.509	86	28.5	134	2.95	8 48	50.4	49 6
3 80 4 97	76 100	20 —40	74—167	1 7—4 7	6 2 11.8	60 31	49—30

FRC functional residual capacity RV = residual volume TC = total lung capacity $\frac{V\ (F_{N_2} = 2\ )}{FRC}$ =

ly low value compared with normals of the same age (66 71 72) The low efficiency in Case 5 may be explained by a hip disease compelling him to use accessory muscle groups during exercise in sitting position. Case 37 had a low mechanical efficiency also during work in supine position and at control tests. She had pronounced lung parenchymal changes and was the oldest in the group The respiratory quotient increased from 0.82 at rest to 0.92 (range 0 82—1 03) during exercise

Alveolar ventilation as indicated by arterial P_{CO} was normal at rest and during exercise The tidal volume increased during exercise to an average of 48 7 (range 32.2— 0 7) % of vital capacity the minute ventilation to 41.9 (range 21.3—68 9) % of MVV The percentage was found to be 68.9 in Case 37 who, as mentioned above had pronounced parenchymal changes and also showed a slight arterial hypoxemia during the work test

The physiological dead space was normal at rest in eight patients. In Cases 5 and 16 it was somewhat higher at rest but showed only a slight increase during exercise to an almost normal value Case 11 had a value slightly higher than normal at rest, which increased to above normal limit during exercise Dead space increased ordinarily during exercise in five patients but in three cases (Nos. 11 23, 37) to a value higher than normal (1) In three patients (Cases 21 27

The diffusion abnormalities were uniformly distributed within the group No marked difference could be perceived between sexes ($p > 0.05$) or between subgroups II a and II b ($p < 0.2$) nor between cases of known long or short duration

Lung volumes (Table 4) Since the first report in 1940 (11) of small lung volumes in cases of sarcoidosis with lung lesions, but without signs of fibrosis, several authors have con firmed this finding. Others, on the contrary have reported normal fun tions in such patients. The construc tion of the groups often makes comparisons difficult In the present ma terial there were generally slightly reduced lung volumes. Two patients (Cases 37 and 38) had somewhat larger residual volumes, both absolutely and in per cent of the total vol ume Similar results were also obtained in comparison with another normal material (53) although the changes are more marked in relatiou to the normal Swedish material used here The reduction of volume was distinct as regards the total capacity and vital capacity and implied for residual volumes, expiratory and in spiratory reserve volume (53) This reduction of volume was more pronounced and uniform in men than in women (VC = $p > 0.2$, FRC $p < 0.001^{***}$ TC $p < 0.02$) No sig nificant difference could be shown between subgroups II a and II b, but there was a tendency toward lower values in subgroup II a Patients with illnesses of known long duration did not differ much from other members of the group

The *maximum ventilatory flows* (Table 6) varied somewhat MVV and also, but to a smaller degree FEV are limited not only by total lung resistance and lung volume but also by muscular strength, motivation and so on. MVV_{free} was reduced signicant ly compared with the predicted values for the whole group and for women ($p < 0.001^{***}$) while the reduction for men was less pronounced and had greater dispersion ($p < 0.2$) No sig nificant differences were found between sexes however ($p < 0.05$) or between the subgroups ($p > 0.8$) nor did cases of known long duration deviate obviously from the group

Nor could significant sexual differences be detected for FEV or MMF The latter part of the expiratory flow seems to be more dependent upon air way resistance than upon muscular power etc The dispersion of MMF is great in the normal material, and the deviations among the patients in this material are not significant FEV % depends more on maximum ventil latory flow than on lung volume In the two cases (Nos. 11 and 19) in which FEV % was significantly reduced, the MVV also showed a cor responding reduction signs of slight disturbances of distribution such as retarded N_2 wash-out (Table 4) were also present

Total lung resistance in pulmonary sarcoidosis (49 50) has been shown to be able to increase owing partly t greater tissue resistance which, how ever dominates the total value only to a small extent, and partly to increased airway resistance Two pa tients (Cases 23 and 2) in the pres

arcoidotic lung infiltrates.

Pa_{O_2} mm Hg	D_{LCO} ml STPD min mm Hg		D_{LCO}/m^2 BSA		D_{LCO} mid capacity l BTPS		$\frac{Q_{sh}}{Q}$	pH units	Standard bicarbonate mE/l	Lactic acid mE/l	Pyruvic acid mE/l	XL mE/l
	Obs.	% of pred.	Obs.	% of pred.	Obs.	% of pred.						
87 92	16.2 23.2	50 50	9.5 14 7	63 81	5.5 8.8	71 83	5.5	7.398 7.373	21 19	1 00 1.89	0 130 0 175	0 34
78 98	21.5 23 5	89 70	13.8 14 9	103 88	8.5 9.3	121 93	1 4	7.397 7.369	23 19	0.91 3 94	0 103 0.243	1 41
86 92	12.9 21.5	53 53	8.1 12.5	37 67	4.0 6.3	33 53	1.3	7 433 7.374	23 20	1 53 4 77	0.153 0.220	2.37
106 83	10.2 25.9	41 66	5 6 14.2	42 71	2.9 9.9	34 84	6 0	7 439 7.380	23 20	1 17 3 72	0 090 0.255	2 41
77 76	14 4 28.8	53 61	7.2 14 4	51 81	7.8 15 6	101 111	4 01	7.399 7.337	21 19	1 61 5.23	0 175 0.278	2 80
90 92	15.5 28 7	101 107	8 4 15.5	103 117	3.2 9 6	100 100	2.0	7 416 7.382	23 19	1 11 3 89	0 090 0.200	1 42
70 71	16.7 27.6	65 78	9.4 15 6	69 86	4.3 7 1	58 67	7 7	7 424 7.336	22 19	1.28 2.89	0 093 0 183	0.40
81 78	17 7 22.1	96 80	11.2 14.0	115 99	6 5 8.2	112 83	4 9	7 403 7.344	22 19	1.50 4.22	0 093 0 203	0 98
66 64	7 1 12 1	70 59	3 9 6 6	75 86	2.0 3 3	50 45	16 0	7.360 7 411	19 21	2 00 4 66	0 123 0 215	1 18
75 84	8.5 21 0	31 86	5.6 13.8	64 103	4.5 11 1	83 131	5 6	7.399 7.322	21 18			
59 79	10 6 20 4	50 60	4 9 9 4	44 55	4 0 7 7	62 73	4.5	7 422 7.379	23 20	1 06 2.22	0 080 0 130	0.30
79 7 59— 108	13 83 7 1 21 5	66 41 101	7 93 3 0 13.6	72 42— 114	5 11 2.0— 8.5	79 30— 121	5.50 1.3— 16.0	7 409 7.360— 7 439	21 9 19— 23	1.323 0 94— 2.00	0 118 0 080— 0 175	
82.6 64 96	23.35 12 1— 28 8	70 30 — 107	13.24 6.6— 15.6	82 38— 117	8.78 3.3— 16 6	86 45— 131		7.364 7.322— 7 411	19.4 18— 21	3 953 1.89— 5 72	0.211 0 130— 0.275	1 421 0.40— 2.80

Q_{sh} blood flow through anatomical shunt, Q = total pulmonary blood flow

(range 0 002—0.33) In two patients (Cases 11 37) with the above mentioned high dead space value during exercise, the quotient V_D/V_T was also above normal limits. In two patients V_D/V_T could not be estimated during work In the remaining eight patients it decreased ordinarily during exercise

The arterial oxygen tension at rest

clusions, the men tend to have a more pronounced reduction of lung volumes, mainly with regard to FRC, *and of compliance the women to have* somewhat lower MVV values, but the relevance of this observation is weakened slightly by the fact that the corresponding relation cannot be shown for other measurements of the ventilatory flow

The decline of W observed and the tendency towards orthostatic reactions have been described earlier in cases of sarcoidosis with bilateral hilar lymph nodes but without lung lesions. The present cases with slight to pronounced lung sarcoidosis present, on *the whole normal central* hemodynamics. No evidence was found that the illness, at this stage causes an impaired venous return owing to intrathoracal pressure variations. Sarcoidotic infiltrates in peripheral vessels (10 45) are rare and can hardly occur to *the same extent as* the blood displacement observed in the present material

Owing to the type and localization of the lung infiltrates (42, 65) varying lung function disturbances are to be expected. Interstitial and intraalveolar changes, *with obliteration* and reduction of lung tissues, peribronchial infiltrate with constriction of the airways, disturbances of the ventilatory flow and hyperinflation, vascular infiltrate with circulatory and diffusional injuries have been discussed theoretically and demonstrated practically in functional studies (13, 50 68 but these have been largely concerned with cases of sarcoidosis and fibro

The present group of patients with lung sarcoidosis without clinical roentgenological signs of fibrosis is *characterized by a tendency towards* reduced lung volumes with reduced compliance and impaired diffusion more or less parallelly In some cases, one or the other component dominates, and individual patients have a more or less obstructive type of func*tional disturbance with ventilation*-distribution impairment, and increased total lung resistance others have a rather pronounced reduction of diffusion. In the majority of the cases, however the reduction of the lung function is moderate at this *stage and does not restrict the oxygen* uptake or working capacity of the patients, which is reduced to a certain extent by the tendency of the patients towards orthostatic displacement of blood

The question of which factors lim*it the working capacity in the pre*sent material can be answered as follows.

1 Ventilation is in no case a limiting factors as indicated by the ($P_{I_{O_2}}$ —$P_{A_{O_2}}$) gradient

2. The diffusing capacity may be impaired to such a degree that it might be a possible limiting factor

3 Although not studied in detail, the work of breathing causing dyspnoea generally does not seem to incapacitate these patients.

4 The oxygen transport capacity during exercise is usually limited by circulatory factors

The diffusing capacity for CO (Table 5, Fig 24) was at rest on an average 13.85 (range 1—21.5) ml/min mm Hg. Six patients with values below the normal limits that were reported earlier by Linderholm (40) and below once standard deviation f r a normal material reported by Donevan *et al* (16) (Cases 5 14 16 23, 27 3) Four of these patients had values below twice SD in Donevan s material (Cases 5 14 27 37) Expressed in % of a value predicted from age and oxygen uptake D_{LCO} at rest was 66 1 (range 41 0—101.3) % The D_{LCO}/ sq.m.BSA at rest was 72 0 (range 42.4—114.3) % from a value predicted also with regard to BSA The D_{LCO}/midcapacity at rest was 87 (range 50 0—121 4) % of a value predicted from age oxygen uptake and midcapacity of the patients lungs

During exercise the D_{LCO} averaged 23.3 (range 12 1—28.8) mm Hg or 69.9 (range 50 0—106) % of the values predicted from age and oxygen uptake The D_{LCO}/m² BSA during exercise averaged 81.5 (range 57.0—116.5) and D_{LCO}/l midcapacity was 85.5 (range 45.2—130.0) % of predicted normal values From the relation to age and oxygen uptake (16) it could be shown that six patients had during exercise values below twice SD from predicted value (Cases 12, 16 23, 2 37 38) two patients had values below once SD (Cases 5 11) If normal values were predicted also with regard to the patients bod surface area five patients (Cases 5 16, 23, 27 37) had values below twice SD and three (Cases 11 12, 38) values below once SD If on the other hand normal values were predicted with regard to the patients lung midcapacity only two patient had, during exercise value below twice SD from predicted normal value (Cases 16 37) and four other patients (Cases 5, 11 12, 27) below once SD

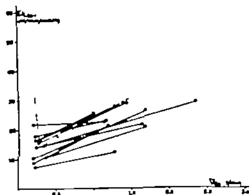


Fig 24 Pulmonary diffusion capacity for carbon monoxide, D_{LCO}, ml STPD/ml mm Hg in rel tion t ygen pt k ($\dot{V}_{O_2}$) ml STPD/min. t rest i pine nd d ring ex rcise i sitti g position. Normal rla tion i thi laborat y (40) indicated by broken lines.

Statistically the difference observed-predicted value was highly significant ($p < 0.001$***) during work. The corresponding difference D_{LCO}/sq.m BSA, was significant ($p < 0.01$**) The difference observed predicted value for D_{LCO} midcapacity during work was not significant ($p < 0.1$)

Maximum Voluntary Ventilation (MVV) Table 6 was determined at a free respiratory rate and at three fixed rates, 40 60 and 80 breaths/min MVV_{free} averaged 108 4 (range 61—177) l/min or 73 % of the predicted value (range 54—111) Two males (Cases 11 23) and four females (Cases 12 14 16 38) had values lower than

4. *Holmgren, A.* Scand. J. Clin. & Lab. I est. *8* suppl. 24, 1956.

25. *Holmgren, A., Jonson, B., Levander, M., Linderholm, H., Sjöstrand, T.* and *Ström, G.* Acta Med. Scand. *158*:413, 1957

26. *Holmgren, A.* and *Li d rholm, H.* Acta Physiol. Scand. *44*:203, 1958.

27. *Holmgren, A., Jonson, B., Linderholm, H., Sjöstrand, T.* and *St öm, G.* Act Med. Scand. *16* :99 19 5.

28. *Holmgren, A.* and *Ström, G.* Acta Med. Scand. *163* 185, 19 9

29. *Holmgren, A., Jonsson, B., Levander, M., Linderholm, H., Sjöstrand, T.* nd *Ström, G.* Acta Med. Scand. *165*:259 19 9

29 *Holmgren, A., J nsson, B.* nd *Sjöstrand, T.* Acta Physiol. Scand., *49*:343, 1960.

31. *Holmgren, A.* and *Orenfors, C. O.* Act Med. Scand. *167*:267 1960.

32. *Holmg en, A.* and *Svanberg, L.* Act Med. Scand. I press, 1961.

33. Huck ber W. E. J. Clin. Invest. *37*:244 19 5.

34. *Kirchheiner, B.:* Act Med. Scand. *168* 223, 1960.

35. *Kj llmer I.* Sandgre I L nd *Biruth G.* Personal communicati ns.

36. *Larsson, H.* nd *Kj llberg S. R.* Acta Radiol. *29* 159 1948.

3 *Leit er S. T. J.* Cardiologia. *10*:379 1946.

38. *Lewallen E. C.* nd *Fowler W. S.* Am. Rev Tuberc. 2 82, 1955

39 *Li derholm, H.* Act Med. Scand. 1.6 413, 19

4 *Li derholm H.* Act Med. Sc nd. *163*:61 1959

41 *Linderholm, H.* Clinical Cardiop lmonary Phy ology Grune nd Stra ton. 1960

42 *Lanyone W. J.* nd *F eiman D. G.* Medicine *31* 1 19 2.

43. *Lovelock F. J.* nd *Stan D. J.* Amer J Med. *15* 4 1953

44 *Lund G.* Sc n. J. Cl n. & Lab. Invest *29* 19.3

45 *Löffl W.* nd *B h n W. J.* H nd buch der Inn Med 4 4 4 1956

46. *Löfgren S.* Act Med Sc nd. *11* 421 465. 1953.

47 *Löfg en S.* Act T b Sc nd ppl. 45 *15* 19 9

48. *Mall ry T. B. B.* 31 4 5 194

49 *Marshall R.* nd *Dubois A. B.* Clin. Sci. *15* 473, 1956.

50. *Marshall R., Smelli H., Boyli S. H. H gl C.* nd *B les D. V.:* Thorax. *13* 48, 1958.

51 *McClement J. H., R.* zelli *A. D. Him melst in, A.* nd *Cournand A.* Amer Rev Tub. *67*:163, 1953.

52. *M rel on C., Fall n, J.* nd *Hick m J. B.* Clin. Res. Proc. *5* 119 1957

53. *Needham, C. D. Rogan, M. C.* nd *M. Donald I.* Thorax. *9*:313, 1954

54. *P ppenheimer J. et al.:* Federati n Proceed. *9*:602, 1950

55. *Ricler W.* nd *Clerk M.* Amer J Clin. P thol. *19* 725, 1949

56. *Riley R. L., Riley M. C.* nd *Hill H. M. D.* Bulletin John Hopkins Hosp *21*: 345, 1952.

57 *Rodewald, G., Bart ls H. B er R. Fleischer E., H Hheinz H. J. Krall J. Wen er J.* nd *B H J.* Pflügers Arch. *126* 565, 1956.

58 *Ross J. R.* nd *Ros B. E.* Act T b. Scand. *33* 49 1959.

59 *Sjöstrand T.* Acta Med. Scand. Suppl. 196, 437 1947

60 *Sm lli H. Apth rp G. H.* nd *M rshall R.* Thorax. *16* 87 1961

61 *Snedecor G. W.* The Iow St t Co lege Press, 1959

62. *Stan P. J. Schwartz, A. F llman J. A* nd *Lovelock F. J.* Am. J Med. *15* 169, 1953.

63. Svanberg L. Sc nd. J Clin. & Lab. I est. S ppl. 25 9 19 7

64 *Th mson A. D.* Postgrad. M J *31*:245 19 5.

65. *U kllnger E.* Beit klin. T berk. *113* 1 1955.

66 *W hlund H.* Act Med. Scand. S ppl. 215, 1948.

67 *T retrerton J. M.* nd *Ger I E. A. J.* Franc Med. et Chi Thorac *8*:33,1954

68 *Will ams M. H.* J. Cl n. I est. *32*:909 1953.

69 Wintrobe M. M. Le & Febiger 1952.

70 *Wright G. W.* nd *F lley G. F.* Amer J Med. *10*:642. 1951

71 *Å trand P. O.* E perimental t dies f phy lc l w rk g capacity i rel t on t sex nd ge M k gaard. 19..

Å trand I. Act Physiol Sc nd. 49 upp 169 1960

FEV %		MMF		MMIF l sec	FIV 1 l	FIV	Compliance l BTPS cm H O	Compliance of predicted from height	Compliance % of pred from VC	Resistance cm H$_2$O l BTPS sec
Obs. %	% of pred.	Obs. l sec	of pred.							
90	101	4 43	101	4.20	3.57	94	0 109	52	78	2.25
86	98	3.19	78	3.32	2.46	86	0 089	68	102	2.06
89	109	5.22	113	9 15	4.88	97	0 142	64	60	1.35
87	99	5.13	124	3.96	3 63	88	0.113	39	86	1.25
73	91	2 61	56	6 60	3 92	93	0.052	37	49	4 06
8	103	3 88	113	7.80	4 44	96	0 134	59	64	1.87
62	78	2.49	57	3 61	3 38	72	0 127	58	56	1.84
72	86	2.60	76	2.98	2.80	77	0 131	85	82	3 02
69	87	1 42	56	4 12	2.79	80	0 081	39	66	3.73
79	9	2 72	84	3.09	2.83	91	0.116	86	92	2 69
86	112	4 64	124	6 64	3.73	96	0.073	23	49	2.79
77 4	99	3 766	94	6 700	4 074	91.8	0 112	49	56	2.328
62 88	78 112	2 48 5.22	57 124	3 61—9 15	3 38—4.88	72—98	0 0 3— 0 142	23—64	49—64	1.28—4 06
80.5	91	3.33	87	3 642	3 012	87.5	0 107	64	81	2.503
69 90	86 101	1 42 3 13	56 124	2.98—4 39	2.46—3.63	77—94	0 051— 0 131	39—85	66 102	1 25—3 73

expiratory olume I one second = FEV % FEV % in per cent of FVC = FEV % Maximum midexpiratory FIV % in per cent of FVC = FIV % Volumes in l BTPS time in seconds.

second expressed in % of forced vital capacity (*FEV*) averaged 79 1 (range 62—90) % or 96 % of the predicted value (range 8—112) One male (Case 11) and one female (Case 19) had values below twice standard deviation from the predicted value Cases 23 and 37 had values lower than once SD (35) The difference observed predicted value for the group however was not statistically significant ($p > 0.3$)

Maximal Midexpiratory Flow (MMF) (38) averaged 3 487 (range 1 42—5.22) l sec or 90 % (range 56—124) of the predicted value. All values fell within twice standard deviation Five patients (Cases 11 19 23, 3 38) had values below once SD from predicted normal value (35) The difference observed-predicted value was statistically insignificant ($p < 0.3$)

Maximal Midinspiratory Flow (MMiF) averaged 5 032 (range 2 98—9 15) l sec The difference between MMiF and MMF was statistically insignificant ($p > 0.02$)

Forced Inspiratory Volume in one second was on an average 3 405 (range 2 46—4.88) l sec, or expressed in of forced vital capacity (FIV %) it averaged 89.5 (range 72—98) %

The forced expiratory volume in relation to *the forced inspiratory volume* FEV /FIV was on an average 0.88 (range 0 4—1 0) % Two pa

Table 1 Case reports in fifteen sarcoidous patients with signs of pulmonary fibrosis

Case no Exami nation period	Sex Age	History	Symptoms		
			First symptoms	Symptoms on admittance	Dysp-noea
4 cases with slight fibrosis					
22 Ma 19 9	♂ 44	X ray normal 194.-51 X ra (routine) 19 2 showed marked patchy densities on both lungs, increasing 1952 -4 then decrease of lesions and from -5 nstant minor lung lesions.	19 2 Slight dyspnoea, tiredness	No ymptoms since 19-4	—
17 March 1959	♀ 54	EN 1934 and 1945. X ray normal 1933-48 (BHL 192-). X ray showed miliary densities in both lungs, increasing 19 1 53, then decreasing nd from -54 constant minor lesions. 19-2 transient renal insufficiency and hypercalcemia.	19-1 Tiredness sear welling, welli	Effort dyspnoea since 19-3	+
29 Feb. 1960	♂ 41	X-ray normal 1947—-3. X-ray 19"2 showed BHL, decreasing to 19-6. Nodula densities in both lungs increasing 19-6-3 but then decreasing and from 19-9 constant minor lesions in both lungs.	19 2 Cough, thoracic pains, tiredness, sear w lling	Effort d spnoea and thoracic pains. Only symptoms since 19-7	
40 March 960	♂ -3	Operated for toxic goiter 1940 Lung X ray normal 1949-52. X-ray 1953 showed BHL and miliary densities increasing to 19-4 but then decreasing and from 1955 constant minor lesions in both lungs. Transient hypercalcemia 19 4	19 2 -3 Sear swelling, thoracic pain	Effort dyspnoea, only ymptom since 19 7	
11 cases with moderate to marked fibrosis					
Dec 19-8	♂ 21	X ra normal 194 -3. Gastric ulcer 1955 X ray (routine) 19-6 showed patchy and coarse linear densities n b th lungs, first increasing, from 19 8 slowly decreasing.			±
1 Nov 19 8	♀ -3	Duodenal ulcers 192 and 1929 I para (1934) EN nd BHL on X ray 19 4 Increasing patchy and coarse linear densities 19-/ -8.	19 4 EN cough, joint w lling and pain, orthostatic complaints	Effort dyspnoea nd thoracic stitch 19-8	
3 Nov 19	49	X ray (routine) 193- howed BHL. EN 1939 when on X ra BHL, patchy nd linear densi ies increasing 1939-4 but then decreasing 19-0- 9 slow increase of coarse l nea lesions in both lungs Right exud pleurisy 194 guinea pig test neg BCG 1940 nd M ntoux since)	1939 EN	Effort dyspnoea from 19 8	
32 Nov 19 9	40	II parae 194 194) X ra normal 1943 4 X ra routine) 19 1 showed BHL nd some parenchymal lesions X ra 1 -/ howed miliary 19 9 creasin coarse linea lesions in b th lungs		Effort dyspnoea, thoracic stitch nd tiredness from 19-/	

BCG Calmette ... BHL ... EN erythema nodosum.

on x ray On admission to hospital four of the patients had more or less acute joint or scar symptoms, ery thema nodosum or fever Three pa tients were quite free from sympt ms, and seven were admitted on findings made by routine x ray examination Roentgen checks made during 1959—60 showed that seven cases had improved considerably two were un changed and two cases were slightly worse

The division of the material into groups was made according to the clinical course of intrathoracal sar coidosis with hilar lymph node reac tion, more or less pronounced lung parenchymal le ions and a chronic stage with fibrosis (17 22, 45) A tudy of the history of the disease from the time it was detected showed that the variations between individu als and during the course of the illness were great and that it was difficult to make a further distinct division of Group II The cases have been reported (Table 1) according to the degree of abnormality in the current roentgeno-grams, and in patients with marked changes on lung x ray there was a tendency towards gross nodular in filtrates. In functional studies of cases of sarcoidosis, division has often been made according to duration of illness Since a feature of the illness is its lack of symptoms, earlier normal lung radiograms are required to determine the actual duration of the condition Distinct symptoms may also indicate that a prolonged but slight sarcoidosis has become acute An idea of the du ration of the illness in each individual case in the present material has been obtained by the comparison of the interval of time between the current period to the last normal or first pathological lung x ray and the first symptoms No certain determination of duration can be made in these cases, although a rough estimate can often be obtained

Group II may for comparison of cases with slight and pronounced changes on the lung x ray be divided into subgroups II a (Cases 12, 38, 16 27 23 and 21) and II b (Cases 11 10 37 14 and 5)

The effect of sex and various types of changes in the parenchyma on the cardiopulmonary function, and the significance of the duration of the condition in this material will be discussed

Hemodynamic studies in cases of lung sarcoidosis without signs of fibrosis have been reported in a few cases at rest and in single cases with light work (51 67) The cardiac in dices are reported as normal, pulmo-nary pressures normal or possibly in individual cases, increase l slightly during work.

The circulatory dimensions in the present material were normal on the whole apart from a tendency towards a reduction of the THb and slight anemia (Table 2)

No distinct difference could be de monstrated between sexes or between patients with slight (subgroup II a) or more pronounced (subgroup II b) changes on the roentgenograms.

Low W $_{70}$ sitting observed were not distinctly correlated to sex ($p > 0.3$) duration or degree of illness, but seem ed to be correlated to orthostatic

Table 1 Case reports in fifteen sarcoidosis patients with signs of pulmonary fibrosis

Case no. Examination period	Sex Age	History	Symptoms		
			First symptoms	Symptoms on admittance	Dyspnoea
13 March 1959	♀ 53	II-parae (1937 1930). X-ray (routine) 1955 showed coalescent patchy and coarse linear densities in *both lungs*. Increasing 19 7-60.	—	Effort dyspnoea increasing since 1955	
31 Sept. 1959	♀ 60	I para (1936). EN iritis and glaucoma 1936 when x-ray showed BHL and co*alescent miliary* densities. Increasing lung fibrosis with shrinkage 1937-52. Cholecystectomy (*PAD = sarcoidosis*) 1949 Left spontaneous pneumothorax 8 month -52, thereafter relatively constant lesions in both lungs.	1936 EN iritis-*glaucoma*	Effort dyspnoea since 1936, last years periods *of bronchitis and then* dyspnoea also at rest.	
31 Oct. 1959	♂ 31	Psoriasis since youth. Syphilis 1950. WR neg. 1934-38. *Lung x ray normal 1948* X ray (routine) 1950 showed BHL and miliary densities in both lungs, increasing 1951 X-ray showed lung fibrosis with some shrinkage	(19 2 periods with effort dyspnoea and cough)	Increasing effort dyspnoea and cough 19 9	
4 Nov 1958	♀ 45	VI parae (1941-44-48-49-52-53). Bilat. chron. kidney dis 1943 45 *Lung* *ray* normal 1945 X-ray (routine) 1949 showed BHL, nodular and patchy densities in both lungs. From 1951 55 increasing lung fibrosis with some shrinkage	(1942 iritis)	Effort dyspnoea, tiredness, thoracic stitch since 1951 orthostatic complaints since 1953.	
41 March 1960	♀ 43	I-para (1950). X-ray 1939-44 showed decreasing BHL and small parenchymal lesions. X ray 1948-60 showed increasing coarse *linear* patchy and miliary lesions Transient hypercalcemia and renal sarcoidosis (PAD) 1957 59	(1935 bronchitis)	Effort dyspnoea and thoracic stitch since -45 bronchitis, period *with d pnoea at rest*	
38 Jan 1960	♂ 41	Systolic heart murmur since scarlatina 1937 but no subj symptoms X ray 1950 -52 showed BHL. X ray (routine) 19 showed nodular and patchy densities Increasing lung fibrosis 19 7-61	*19 0 transient* effort dyspnoea, cough and fever	*Periods of bronchitis* thoracic pains and increasing dyspnoea since 19 7	
18 March 19 9	♂ 59	Bilat iridocyclitis 1931 X ray 19 1 showed BHL, miliary nodular and coarse linear densities in both lungs. Successively increasing lung fibrosis and shrinkage 19 1 Hypercalcemia and renal sarcoidosis (PAD) from 19 4	1951 iritis	Effort dyspnoea since 1952, bronchitis periods, *increasing dyspnoea* and thoracic pains from 19 4	

dicates that a slight disturbance of the ventilation perfusion relationship was present A rather high V_D/V_T during work was shown in two of the three cases mentioned above (Cases 11 and 37) in which retarded N wash-out could also be demonstrated Case 37 had, at rest, an increased intrapulmonary shunt (57) and a minute ventilation that was 60 of MVV_{pred} The gross efficiency of ventilation expressed as the conductance of the air ways for oxygen $V_{O_2}/(P_{IO_2}—P_{AO_2})$ averaged 32 6 (range 23.2—49 9) ml STPD min/mm Hg at work, values of the same order as can be calculated from normal data in the literature and as in patients with BHL (40 41)

The *diffusion capacity* for CO was low both at rest and during work (Table 5) Of the five patients (Cases 5 16 23, 27 and 3) in whom a significant reduction was present in relation to the normal value calculated with reference to body surface area one (Case 23) had a normal value in relation to lung midcapacity and two (Cases 5 and 27) had only slightly reduced values in this relation It seems likely that the function should be affected differently according to where the sarcoid granulomata are situated in the lungs — peribronchially interstitially perivascularly etc (42 65) The cause of the decreased diffusing capacity may be quantitative, decrease of the D_L due to a loss of alveoli or qualitative decrease due to a change in the diffusion distance and or membrane permeability for CO or oxygen This investigation showed that the D_{LCO} was low in relation to the body dimension and also in relation to the dimensions of the lungs The study of the lung volumes on the other hand, has, however shown that they were decreased

There seemed to be a certain co-variation between the reduced lung volume and the impairment of diffusion, but even with regard to the observed midcapacity there was a distinct reduction, although the decline during work was more dispersed and not statistically significant ($p < 0.1$) The sarcoidotic infiltrate could not, however be generally regarded as producing a "lobectomy (50)

The D_{LCO} test was carried out during work sitting, and the orthostatic displacement of the blood volume could possibly have been expected to give a decreased capillary blood volume and possibly a reduction of the diffusion capacity Three cases with pronounced orthostatism (Nos. 5, 11 and 12) had slightly reduced diffusion in both positions, however No cases had such a degree of anemia that low concentrations of hemoglobin could significantly affect the diffusion values.

In a few cases, it seems possible that diffusion may have been a factor limiting a further increase of the oxygen uptake during work. The alveolo-capillary oxygen gradient (P_{AO_2} — $P_{\bar{c}O_2}$) averaged 51 4 (range 32—85) mm Hg during exercise The cases reported here were not examined during maximum work, but four of them (Cases 5 16 23 and 37) showed gradients of 66 62, 66 and 85 mm Hg respectively or significantly higher values than those reported in normals. (40)




Fig 1 a. C 22, 17 11 1953 Marked nodu l nd coalescent pat hy densities in both l ngs.

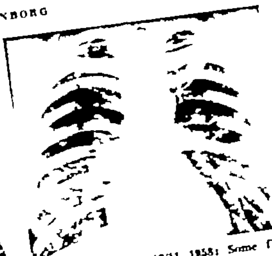


Fig 1b C 22, 13 11 1958: Some fine linea den ities l both l gs.



F g 2 (1 12 1 M l ry d gs l h l e




F g 2 b C 17 12 3 19 9 Some f l nea d n ities n both l gs.

ent material had significantly increased total lung resistance slightly reduced FEV but relatively low values for MMF and reduced compliance Case 23 had a central atelectasis in the right lung and generally small lung volumes, Case 37 (see above) retarded N wash-out somewhat impaired alveolar ventilation during work, when V_E was 60 % of the patient's $MVV_{(ind)}$ and a somewhat increased FRC.

Compliance (Table 0) was, in relation to normal values calculated either from height or observed vital capacity significantly reduced in seven patients Two cases (Nos. 12 and 37) were low only in relation to the value calculated from height, two more patients (Cases 5 and 21) had slight reduction also in comparison with the value calculated from vital capacity For some months, Case 12 had had BHL and a few lesions in the lung parenchyma on x ray small lung volumes, reduced MVV and a slightly reduced diffusion. Case 37 a woman fifty-eight years old, with widespread parenchymal filtrates and pronounced functional disturbances, has been reported above Case 5 had, on the x ray pronounced parenchymal filtrates of rather uncertain duration, pronounced orthostatism, reduced lung volumes and a slightly impaired diffusion Case 21 had moderate lung lesions of uncertain duration, slight orthostatism, small lung volumes but otherwise more or less normal function. In February 1960 after the x ray *was normal, this patient contracted* indefinite symptoms and hypercalcemia which was not permanently improved by corticoid treatment Later the patient proved to be suffering from a localized hypernephroma in the left kidney confirmed by operation in July 1960 The slight functional disturbances demonstrated were little pronounced, even in relation to the patient's sarcoidosis, so the possible occurrence of the kidney complaint at the examination in question is without significance from the point of view of heart lung function

Compliance was significantly reduced for the whole group in comparison with the normal value calculated from height or from the vital capacity observed ($p < 0.001$***) The latter reduction was more pronounced for men than for women ($p<0.001$***) while no significant difference could be observed between subgroups II a and II b ($p > 0.8$) Subgroups II a and II b showed a uniform decrease also in comparison with the values calculated from height ($p > 0.9$) The men had, in this case too lower values than women, but the difference was not statistically significant ($p < 0.1$) Individual patients with illness of known long duration (Cases 14 16 and 23) did not deviate markedly from the group or from cases of short duration (Cases 12, 27 and 11)

Varying functional results have been obtained in the eleven cases No distinct differences could be detected within the group regarding the frequency of infiltrates on the lung roentgenogram, nor was there any marked relation between examination *results and roughly assessed duration* of illness In the present material which is too small to justify final con

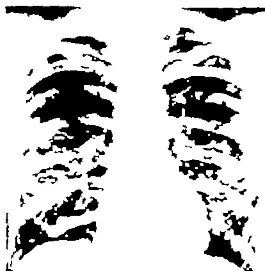


Fig a. C 7 21/11 1958 ... pat by d ... arse lines d ... ities, mainly in the midpart f lung



Fig 3 b. C 7 15 9 1960. Decrease of l g lesion ince 1958 but som increase f co rs lines densities.



F ... 1 C arse l ea nd p t h d ... t es w h tic l ... rr g me t b th l ... l ... l eme t Pr nounced ght ... h l re

was planned to allow of a thorough analysis of the cardiovascular and respiratory functions in sarcoidotic patients with pulmonary fibrosis of different degrees at rest and at work.

Material and methods

The material consists of fifteen patients who, on the basis of clinical and roentgenological examinations (aa) could all be shown to have or to have had earlier marked lung lesion and who at the time of the investigation had roentgenological signs of light moderate or marked pulmonary fibro-

Summary

11 patients, 5 men and 6 women, with sarcoidotic lung infiltrates but without signs of fibrosis were investigated with regard to the cardiopulmonary function

Dimensions of the circulatory system did not significantly differ from what is found in normals

Working intensity at a pulse rate of 170 beats/min in sitting position was lower than predicted from the circulatory dimensions. In supine position the pulse rate on a given load was lower than in sitting.

Cardiovascular function, studied at rest and during exercise with right heart catheterization did not significantly differ from what is found in normals Four cases showed a slightly high pulmonary vasculatory resistance during exercise

Static lung volumes were somewhat low in six cases, lung compliance was low in five of these and in two further cases Two cases had a slightly high total lung resistance

Ventilation was normal in nine cases, two showed a somewhat impaired distribution, an increased total lung resistance and one an increased dead space ventilation

Blood gases during exercise were normal except for a low P_{aO_2} in one case with ventilatory disturbances.

Diffusion capacity was decreased in six cases Three had a somewhat high anatomical shunt

Oxygen transport capacity during exercise was mainly limited by circulatory factors. The lower capacity for work in sitting position could be explained by an increased effect of gravitational shifts of the blood seemingly due to lower venous tone

References

1 *A m s F* nd *Mel en M* Act Phy iol Sc nd. *38* 1, 1956
2. *Ba k S R.* nd *S mm rson W* J Biol Chem. *138*.535 1941
3. *Bart l H* nd *Rodewald G* Pflüg. Arch. *256* 113, 1952.
4 *Bart l H Böcherl E., H rt C. W Rodewald G* nd *Schwab M* Spring Verlag, 1959
5 *Beckl k M R* Thorax, 7 111 1952.
6 *Berggren S M* Act Phy i l Scand. 4, ppl 11 1942.
7 *Bevegård S., Holmg en A* nd *J sson B.* Act Phy i l Scand *49* 279 1960
8. *Bjö kman, S.* Beit Tuberk. *88*:619 1936
9 *Boothby W M Lundin, G* and *Helmholt H F* Proceed. Soc Exper biol. *67* 558, 1948
10 *B tt he E.* Am. A. Arch. P th. *68* 75 1959
11 *Bruce T* nd *Wass E.* Acta Med Sc nd. *104* 63, 1940.
12. *Ca lens F* Diseases f Chest, *36* 343 1959
13. *Coates F O* nd *Comroe J H* J Clin. I vest. *30* 848, 1951.
14 *Cugell D W M Ls A Elliot M F Badger T L.* and *Gaensl E. A.* Amer Rev Tuberc. *74*:317 1956
15 *Dan l A C.* Dise ses f Chest, *16*:360, 1949
16. *Donovan R E., Palm W H Farma, C. J* nd *Bates D. V* J Appl. Physi l. *14* 483, 1959
17 *Dressl M* Spri ger Verlag, 1942.
18. *Ehrner L.* nd *Nis H O* Act Med. Scand. *164*:98, 1959
19 *Ehrner L.* Acta Med. Scand. ppl. 353, 1960.
20 *Harri J A* and *Benedict F.G* Carnegie I st. W sh. Publ. No. 279 1919
21 *Granath A Jonson B.* and *St andell T* Acta Med. Scand. *169* 125 1961.
22. *Gravesen P B* Andelsboktrykeriet, Od nse, 1942.
23. *Grimby G* nd *Söd holm B* Personal mmu ic tions, 1961

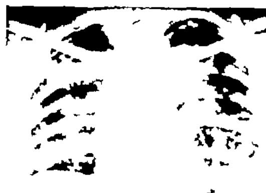


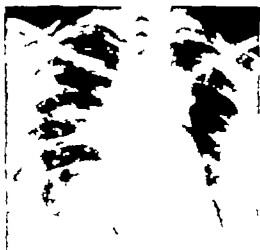
Fig 9 a. C 15 9 3 1957 Coalescent pat hy nd coarse linea den ities i both l gs. Pleural f d ment



Fig 9 b C 15 20 2 1959 Coarse li nd pat hy de ities nd me hri k ge i both l gs. Pleural i l eme t



Fig 10 a (31 7 9 1956 BHL, coalescent mili ry nd d l nd some li den i ties in both l g



F g. 10 b C 31 10 7 19 9 Coarse line de ities nd parse ccalat re i both l gs, hrink ge of left pper lobe hil d formit nd pleural i l m t

STUDIES ON THE CARDIOPULMONARY FUNCTION IN SARCOIDOSIS

III

Cases with fibrosis of the lungs

By

NILS SVANBORG

From a clinical point of view the unpredictable prognosis of the early stage of pulmonary sarcoidosis has been stressed (22, 54). On the other hand it is a well-known fact that cases with chronic sarcoidosis may develop severe cardiopulmonary insufficiency. Studies of the pulmonary function in patients with sarcoidosis of the lungs and lung fibrosis have been published by several authors (2, [illegible] 17, 18, 51, 61, 62, 64, 65, 72, 73, [illegible] 85, 88, 91). Reports of studies on the central haemodynamics and oxygen transport capacity in the disease are few however. One investigation reports impaired diffusion and arterial and an increase in cardiac output (3) in five patients with slight pulmonary fibrosis with restrictive disturbances of the pulmonary function. Two other patients with severe fibrosis had small lung volumes but more pronounced disturbances, impaired distribution and increased residual volume. In other reports (2, 18, 62, 72) some patients with severe fibrosis showed an increased pulmonary arterial pressure.

Previous investigations have mainly studied patients from [illegible] the disease with severe fibrosis. Some have emphasized a tendency to obstructive function on bronchospirometry (17, 62, 74), others report fibrosis pattern with restrictive function and disturbances (4, 61, 62, 7). Low diffusion capacity has often been found in sarcoidosis, especially in cases in the fibrotic stage (2, 8, 61, 62, 72, 73, 74). Other workers have found that pulmonary fibrosis, even though extensive, may fail to give measurable evidence of impaired respiratory function (46, 88). The parenchymal changes in chronic sarcoidosis may be fibrotic but with different localization and different functional consequences. The pattern and distribution are probably of more significance than the degree of fibrosis. Impaired function in patients with sarcoidosis whose lung x-ray shows full improvement seems to confirm this (61, 78).

In earlier reports the cardiopulmonary function in patients with BHL and with parenchymal infiltrations has been studied. The present report

Reason for admittance		Clinical investigation				Time interval (months) from			X-ray fig. no.	Previous treatment Clinical course
Symptoms	X-ray	SR mm 1 h.	Mantoux	Electrophoresis	Other findings	Last normal X-ray	First path. X-ray	First symptom		
—	+	1	—			96	81	(81)	1 a-b	—
+	—	11	+	γ = 1.8		131	88	93	2 a-b	Steroids 2 months 1932. Improvement on X-ray 1934
+	—	14	+	(γ = 1.6)		141	93	96	3 a-b	Steroids 3 months 1936 Improvement on X-ray 1935
—	—	4		γ 2.1	White blood cells in 4,5 eosinophils	96	75	80	4 a-b	Vitamin D 1 month 1934 Steroids 5 months 1935, without improvement during therapy
—	+	2				70	28		5 b	Without treatment improvement on X-ray 1935-60.
+	—	24	—	γ 2.2			47	48	6	Without treatment slight improvement on X-ray 195.-60.
—	—	18	+	γ 1.8	blood pressure 140/80		235	228	7 b	Vitamin D_2 2 months 1950 with slight improvement? on X-ray Digitalis in period 1958.
—	+	21	—	γ = 2,1	AS = 280	172	104	(30)	8 a-b	—

AS = antistreptolysin titer AST = antistaphylolysin titer WR = Wassermann reaction.

Table 9 Some anthropometric data in sarcoidous patients with sign f pulmonary

Case no	Sex	Age years	Height cm	Weight kg	BSA, m²	BMR	Bl d vol. ml	THb g	THb/kg	Hb conc. g/100 ml
4 cases III slight fibrosi										
22	M	41	183	89	2.10	3	1010	1065	11 97	11 0
17	F	34	172	66	1 68	18	345	500	8 82	13 2
29	M	41	174	83	1 97	4	590	45	9 7	13 2
40	M	43	1 0	83	1 93	10	675	810	10 12	1 2
11 cases moderate to marked fibrosi										
7	M	31	186	69	2 01	10	73	0	11.32	13 5
1	F	33	160	66	1 8	2	63	460	6 97	11
3	F	49	169	61	1 2	63	810	575	9 43	11 2
32	F	40	165	58	1 61	9	380	465	8 30	13 1
1	F	43	18	63	1 71	20	360	490	7 8	11
31	F	50	164	63	1.68	0	90	493	70	11 1
34	M	33	178	65	1 83	4	760	615	10 69	13 2
4	F	4	168	54	1 6	16	508	5	10 28	12 3
41	F	4	161	72	1 7	16	75	615	8 96	12 8
36	M	44	168	76	2 02	13	800	35	9 53	11 0
18	M	20	162	50	1 2	20	473	310	10 70	11 8
M		31	178 0	61 8	1 835	6 8	672 5	682 5	10 1	12 2
Range		29 41	16 186	0 6	1 33 2 01	10 20	1 800	310 770	0 97 11 32	11 8 14 5
M		1 0	164 6	63 1	1 677	18 0	610 0	2 0	8 49	11 7
Range		10 53	160 169	1 2	1 60 1 75	0 63	0 810	460 615	6 9 10 2	11 0 12

BSA body surface area THb total amount of hemoglobin BMR basal metabolic rate in per cent of pr moderate to marked fibrosi

11.3) g/kg. The females had 8.10 (6.0 –10.3) the males 10.3 (9.9 11.3) g/kg, which is slightly low in three females (cases 1 14, 31) and in two males (cases 18 36). The difference from a value predicted from height was not statistically significant for the whole group or for group III b (p > 0.2). One male in group III a (Case 34) and one male in group III b (Case 18) had low hemoglobin concentration and should be classified as anemic (8). Three more patients (cases 3, 31 34) showed slightly low value. One patient (Case 11) had a slightly high value.

Blood volume (Table 9) was on an average 2 (range 6 3 8 1) ml/kg body weight in group III a and 1 (range 2 1 9 0) ml/kg in group III b. One male in group III a (Case 40), three females and one male in group III b (Cases 1 14, 32 36) had slightly low values but none of them differed significantly from the normal values earlier reported from this laboratory (36).

Heart volume in per n l ilion in

Reason for admittance		Clinical investigation				Time interval (months) from			X-ray fig. no	Previous treatment Clinical course
Symptoms	X-ray	SR mm/1 h	Mantoux	Electrophoresis g%	Other findings	Last normal X-ray	First path. X-ray	First symptom		
+	—	10	—	$\beta = 1.0$ $\gamma = 1.8$	AS = 400		42	(30)	9 a-b	Steroids 5 months 1954 without improvement on X-ray
+	—	73	—	$\gamma = 2.1$	Slight dy pnoea at rest. Low frequent ejection murmur in second left intercostal space Coarse rales descrete i both lungs. AS = 800		279	279	10 b	Digitalis since 1958 and slightly less dyspnoea.
+		4	+	β 0.93 $\gamma = 2.5$	Slight psoriasis WR neg. AS = 6400 – 1600	163	117	(84)	11 -b	—
+		14	±	β 1.03 $\gamma = 2.6$	Vesico-bronchial breathing sound, no rales AS = 400	136	118	(180)	12 -b	Periods with bronchitis and increase of dyspnoea 1958 61 Lung ray unchanged.
–		33	+	$\beta = 1.13$ $\gamma = 3.0$	Accentuated, pulmonic component. Blood pressure 163 93 Uric acid = 6,8 AS = 400		232	232	13 b	Vitamin D_2 and steroids 2 months 1957 without improvement on X-ray
+		31	+	$\beta = 1.13$ $\gamma = 2.7$	Accentuated and split pulmonic component. High frequent regurgitation murmur over the apex Uric acid = 8 4 AS = 400		123	123	14 -b	Vitamin D 3 months and steroids 6 months 1958 with slight transient improvement on X-ray
+	—	78	—	= 0.5 $\alpha_2 = 0.9$ $\beta = 1.1$ $\gamma = 2.9$	Accentuated pulmonic component. Coarse rales descrete in both lungs. Thymol = 9 AS = 1100 Uric acid = 7,2 Serum calcium = 13,2 10,2		87	88	15 a-b	Transient improvement on X-ray during steroid treatment 7 months 1955–56. No improvement of steroids or digitalis 1959 impaired and died in cardio-pulmonary insufficiency July 1959

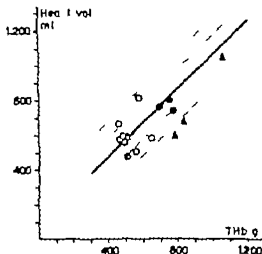


Fig. 16. Heart vol me ml, (ordinat) I re I tion t tot l amou t of hemoglobi (b- sci sa) Triangles represent gro p IIIa, ci les group III b. Filled symbol represent males nd pen ymbol fem les. Stra ght li represent normal regres ion line described by H lmgren *et al.* 1957 Broken lines indicat ± t nd rd rror f estimat nd twice t ndard rror f estim t

During and after the work test ECG was normal in eight cases. One patient (Case 7) showed supraventricular extrasystoles on the highest work load. Two more patients (Cases 31 20) had isolated ventricular extrasystoles during exercise.

Orthostatic test (Table 2). In upright position one patient in group III a showed a very marked increase in heart rate to 140 beats/min (Case 17), the others showed an increase of less than 20 beats/min. In group III b two patients (Cases 7 31) showed a very marked increase in heart rate to 120 and 132 beats/min respectively; six other patients (Cases 1 4 15 18, 34 30) had a marked increase to 100 106 120 124 110 and 125 beats/min respectively. Only three patients (Cases 3 32, 41) had an increase in pulse rate of less than 20 beats/min.

From the relation between pulse rate standing and the ratio height THb[1] it could be shown that in five patients (Cases , 17 18 31 36) the values fell above twice. In three more patients (Cases 15 34 41) above once standard error of estimate in a normal material earlier reported from this laboratory (34).

Working capacity sitting (74 84) (Table 2). All patients in group III a could perform work increasing the heart rates approaching or above 170 beats/min. In group III b five patients (Cases 1 4 15 18, 41) stopped working at a pulse level of 152—164 beats/min. In these cases an extrapolated value for W_{170} was used only for comparison with other parameters. In the relationship between W_{170} and heart volume (Fig. 17) one patient in group III a (case 1) and four cases in group III b (Cases 3, 31 34 30) showed values above twice standard error of

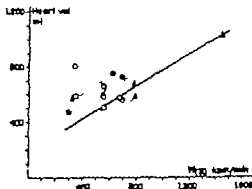


Fig. 17. Heart l me ml, (ordinat) l re l t t rat f work t pulse rat f 170 beats/min. (W_{170}) kpm/min. (absci sa) S mboles as n Fig. 16.

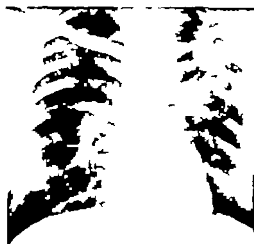


Fig 3 C 39 25/11 1957 M ked nd la nd p t by d nsities i both l gs.



Fig 3 *b* C 39 23 2 1960 Some line nd nod l den ities i both l ngs. Slight pleural i olveme t



Fig 4 a. C 40, 2/11 1954 M ked m liary densities i both lungs.

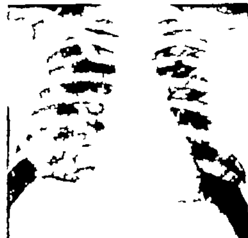


Fig. 4 *b.* C s 40, 17/3 1960 Moderate coa se line densities i both lungs. Pleural involvement.

Table 3 Observations during heart catheterization in 15 sarcoidosis patients with signs

Case no.	Catheterization no.	Work load kpm/min	Pulse rate beats/min	Oxygen uptake ml/min	Mechanical efficiency per cent	Ventilation, l (BTPS)/min	Ventilation l (BTPS) per oxygen uptake l (STPD)	O_2 capacity, ml/100 ml	O_2-sat., per cent B A	PA	AV O_2-diff ml/l	Cardiac output l/min
4 cases with slight fibrosis												
22	45/59	Rest	60	298		8.31	27.9	18.0	98	76	44	6.8
		600	112	1690	20.6	41.78	24.7	19.4	98	48	102	16.6
		900	134	2339	21.1	60.68	25.9	20.2	98	43	114	20.5
17	29/59	Rest	94	207		6.10	29.5	16.2	100	75	37	5.6
		200	144			24.28		16.2	98	54	71	
		400	164	1232	18.6	39.62	32.2	16.8	95	38	97	12.7
39	12/60	Rest	74	293		8.05	27.2	14.6	98	72	39	7.5
		200	116	904	12.6	23.83	26.5	16.3	97	55	67	13.6
		400	130	1217	20.7	33.83	27.8	15.7	97	46	78	15.7
40	16/60	Rest	80	280		8.78	31.1	19.6	97	76	41	6.8
		200	102	806	18.3	21.91	27.1	19.9	96			
		400	124	1081	22.8	32.31	29.8	20.3	95	55	82	13.2
		600	160									
11 cases with moderate to marked fibrosis												
7	78/58	Rest	94	334		12.09	36.2	18.3	98	80	36	9.2
		300	121	860	27.2	24.66	28.6	18.7	98	60	74	11.7
		600	144	1305	27.0	38.93	27.9	19.1	97	51	89	15.0
1	63/58	Rest	87	212		7.24	32.4	15.1		78	34	6.3
		200	118	762	17.4	21.33	28.0	15.8		51	76	10.0
		400	142	983	24.6	31.79	32.3	16.0		42	89	11.1
3	69/58	Rest	106	335		11.03	32.9	16.1	97	76	34	10.0
		100	124	647	15.4	20.22	31.3	15.2	98	62	57	11.3
		200	126	829	19.4	23.49	28.3	15.4	96	57	60	13.6
32	76/59	Rest	72	235		7.29	31.0	14.2	98	7	34	6.9
		200	121	818	16.5	24.39	29.8	14.8	99	63	67	12.2
		400	156	1203	19.7	40.84	33.9	16.6	98	47	83	14.5
15	22/59	Rest	106	252		7.46	29.6	16.6	99	81	31	8.1
		200	130	784	18.0	22.77	29.0	16.2	99	58	71	11.0
		400	144	1092	22.7	37.56	34.0	16.9	97	47	89	12.3
31	74/59	Rest	107	249		7.50	30.1	15.2	93	73	33	7.5
		160	147	700	16.0	18.72	26.7	16.3	83	44	60	11.7
		300	164									
34	82/59	Rest	75	294		10.58	36.0	16.5	97	75	34	8.6
		300	116	1004	20.2	27.73	27.7	17.5	89	44	81	12.3
4	73/58	Rest	82	312		10.63	34.1	16.2	98	76	38	8.3
		200	108	661	27.5	17.78	26.9	16.6	98	58	71	9.4
		400	127	904	32.3	29.41	32.5	17.2	97	46	90	10.1
41	21/60	Rest	70	274		9.31	34.0	17.2	92	69	42	6.5
		100	106	719	10.6	23.21	32.3	18.0	94	49	84	8.6
		200	120	924	14.8	30.49	33.0	18.0	93	43	96	9.6
36	4/60	Rest	92	327		11.60	35.5	17.6	95	73	36	9.0
		200	148	1104	19.4	37.35	33.8	18.0	86	40	85	13.0
18	32/59	Rest	[illegible]	270		11.04	40.9	14.8	100	70	43	6.0
		100	[illegible]	607	14.3	31.02	51.1	15.8	89	44	70	8.7

B A = brachial artery PA … onary … ery PCV pulmonary capillary …ous pressure RA right





Fig 7 *a*. C 3, 16 4 1948 Gros nod la nd patchy oalesce t den ties i both l g

Fig 7 *b* C 3, 28 10 1958 M l ly oarse ll ea de ties, pleural lov l ment

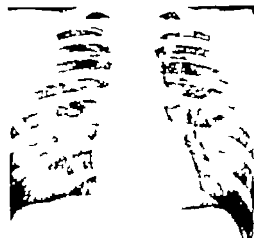




Fig 8 *a*. C 32, 29 4 1957 M liary nd some l ea densities l both l ngs.

Fig 8 *b* C 32, 11/11 1959 Moderat coar se linear nd pat hy den lifes. Some pleural lnv l ement

plications except for occasional premature beats and in one patient a transient right bundle branch block (Case 15). Hemodynamic data obtained in connection with the heart catheterization are presented in Table 3.

Pulse rate at rest was 77.5 in group III a (range 60—94) beats/min. and 89.2 in group III b (range 70—107) beats/min.

Oxygen uptake was 15.5 (range 11.0—17.2) per cent of predicted basal value at rest in group III a and was slightly higher than the BMR. In group III b $\dot{V}_{O_2}$ at rest was on an average 39.7 (range 12.8—91) per cent higher than predicted basal value or markedly higher than the BMR both for men and women.

During exercise the oxygen uptake increased with increasing working intensity corresponding to a mechanical efficiency (84, 92, 93) of 21.1 (range 18.6—23.8) % in group III a (highest load 400—900 kpm/min.) and in group III b to an average of 20.3 (range 12.4—32.3) % on the highest work load (100—600 kpm/min.) increasing the heart rate to 117.0 (range 116—164) beats/min. The rate of work at a given pulse rate was higher during catheterization than in sitting position without heart catheterization but lower than in supine position (Fig. 19) without heart catheterization.

Right ventricular pressure. The systolic pressure at rest was 25 (range 20—31) mm Hg in group III a and increased during work within normal limits. The end-diastolic pressure at rest was 5.5 (range 1—7) mm Hg but increased slightly during exercise in contrast to the usual findings in younger normals but within the limits for older normals earlier found in this laboratory (28, 30). End-diastolic pressure during exercise averaged 8.0 (5—10) mm Hg.

In group III b the systolic pressure was on an average 28.0 (range 17—48) mm Hg. During exercise it increased with increasing load to 54.1 (range 28—84) mm Hg or above normal limits in five patients (Cases 3, 18, 31, 38, 41). End-diastolic pressure at rest was on an average 2.2 (range —2, +6) mm Hg and increased slightly during exercise to an average of 6.0 (range —2, +14). Two patients (Cases 3, 31) during exercise showed values slightly high as compared with the younger, but within the limits for the older normals.

Pulmonary artery pressures. In group III a the systolic pressure at rest was 23.3 (range 17—31) mm Hg. The corresponding figures for mean and diastolic pressures were 15.8 (range 13—20) and 10 (range 0—12) mm Hg respectively. The mean pressure during exercise in group III a increased within normal limits.

In group III b the systolic pressure in the pulmonary artery averaged 27.5 (range 16—40) mm Hg. The corresponding figures for mean and diastolic pressures were 18.1 (range 11—32) mm Hg and 9.5 (range 6—17) mm Hg. During exercise the mean pressure increased to an average of 37.0 (range 13—54). Six patients (Cases 3, 18, 31, 34, 36, 41) showed significantly high values during work. No significant pressure gradients over



Fig. 11 a. C 34 15/11 1931 M rked mili- ry nd some nod l den ities i both l gs. Pleural i ol em t



Fig. 11 b. C 34 6/10 1939 Coarse linea den ities i both l gs, hri k g f l ft nd some shri kag of right uppe l be Ba- l emphysem especi lly i left l g. Pl ral i volvement.



Fig. 12 a. C 4, 29/9 1933 Nod la nd p tchy densities i both l gs.



Fig. 12 b. C 4, 2/12 1966 Coarse linear nd pat hy coalescent de sities, partly with reticul arrangement. Some shri kage pl ral in l ement

normal materials from this laboratory (11 39).

A study of the relationship between ($\bar{P}_{PA} - \bar{P}_{PCV}$) and cardiac output (Fig. 20) showed that one patient in group III a (Case 40) and seven patients in group III b (Cases 3, 4 18, 31 34 36 41) had values significantly higher than those computed from a normal material earlier reported from this laboratory (11 39). Two more patients had slightly high values during exercise (Cases 15 32).

Right atrial pressure was recorded normal at rest in thirteen patients and was omitted in two patients.

Brachial arterial pressure. In group III a the systolic pressure was on an average 100.5 (range 104—124) mm Hg. Corresponding values for mean and diastolic pressures were 89 0 (range 84—100) and 0 0 (range 62—8) mm Hg. The pressures all increased normally during exercise.

In group III b brachial arterial pressures were recorded in ten and omitted in one patient. At rest the systolic pressure was 12 (range 109—1 3) mm Hg, the mean pressure 93.4 (range 78—124) mm Hg and the diastolic pressure 69 9 (range 60—89) mm Hg. The pressures increased normally during exercise with increasing load. The pressures on the highest work loads were on an average systolic 165.2 (range 132—196) mm Hg, diastolic 85.3 (range 66—104) mm Hg and mean pressure 116 0 (range 92—142) mm Hg. The pressures at rest were slightly high in one patient (Case 3) and significantly high in another (Case 41) in comparison with the values for both younger and older normals (28, 39). Case 3, who also had a high BMR, was shown to have a slight hyperthyreosis. Case 41 like several other patients in this group had earlier had a renal sarcoidosis but had at the time of the present study no signs of renal involvement except for a borderline value of uric acid (57).

All the patients mentioned above with an increased right ventricular systolic pressure showed an elevation of pulmonary artery pressure and an increased pulmonary vascular resistance. No patients had a significantly elevated PCV mean pressure during work. The above mentioned slightly high values (Cases 1 3, 15, 36 41) might fall within the limits for normals of the same age. One of these patients (Case 31) had a low frequent ejection murmur probably of pulmonic origin, another (Case 36) had an accentuated and split pulmonic component and since scarlet fever 1927 a high frequent regurgitation murmur over the apex as a sign of mitral incompetence but no signs of mitral stenosis clinically or in phonocardiogram.

Arterial oxygen saturation (Table 3) in group III a was at rest on an average 98.5 (range 97—100) % and decreased insignificantly during work to 98 4 (range 95—98) %. In group III b the corresponding value at rest was 96.8 (range 92—100) % decreasing during exercise to an average of 92.4 (range 83—98). Simultaneously the O_2 capacity of arterial blood increased on an average by 1.3 vol. per cent in group III a and 0.88 vol per cent in group III b. In group III a



Fig 15 a. C 18, 15 9 1954 Coarse line nd some patch densities i both l gs.



Fig 15 b C 18, 21 4 1959 I both l ngs coarse line pat by coalesce t densities shrinkage pleural invol ement, mphysema. Soft tis enlargement bil teral in the p- pe mediastin m.

sis In all cases th liagnosis was supported by lymph node biopsy from the supraclavicular fossa (19) or the mediastinum (16) Repeated gastric lavage and lymph glan l m terial tested f r tuberculosis on guinea pigs an l cultures were negative

The procedure and methods have recently been reported (Holmgren Svanborg, 1961)

All casuistic l ta of significance have been collected in a case report in Table 1 The patients had a mean age of 44.3 (range 29– 54) ears, seven were males, eight females Patients who had only minor signs of fibrosis on lung x ray have been lescribed separately in group III a those with moderate to marked fibrosis in group III b In the tables the patients were arranged according to increas ng degree of roentgenological ly determined fibrosis. Most patients have been hospitalized several times for their disease and all but one (Case 22) were in hospital for at least a f rtnight, during which time the study was performed

Results

BMR (Table 2) in group III a was + 1.5 (range — 10 + 15) per cent and in group III b + 13.9 (range — 10 + 63) per cent of the predicted normal value (31) One patient (Case 3) had a significantly high value and was shown to have a slight hyperthyreosis.

Total amount of hemoglobin (Table 2) was 10 1o (range 8.9—12 0) g/kg body weight in group III a In two patients (Cases 39 40) THb was slightly lower than that ordinarily found (34) The corresponding values in group III l were 9.23 (range 7 0—

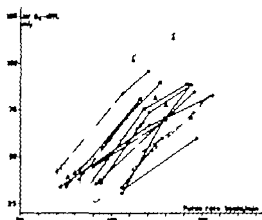


Fig 23. Arterio-venous ox ge difference ml/l in relati n t pulse rate beats/min. t rest and d ring work. Symbols a i Fig. 21

for cardiac indices were 3.22—3.88 in group *III a*, and 3.71—3 81 *l/min/m²* BSA in group III b

During exercise the cardiac output increased in group III a to between 12.7 and 20.5 l/min and in group III b 8 7—15.0 l/min. The increase lies in relation to increasing $\dot{V}_{O_2}$ within normal range in all patients except one (Case 3) who at the highest load showed a slightly high value (Fig. 24)

Stroke volume at rest in group III a averaged 89.5 (range 59—114) ml or 1.51 (range 1 44—1.60) % of the blood volume and 12 64 (range 10 09 —16 78) % of the heart volume

The corresponding values in group III b were 80 0 (66—115) ml or 1 90 (1.53—2.53) % of the blood volume and 14 14 (10 09—20.20) of the heart volume

During work the troke volume in group III a was higher than at rest at the highest load it averaged 20.5 (range 22—34) % al ve resting value Thus during work th str ke volume increased to 1.8 % of the blood volume (11 30)

The stroke volume in group III b decreased on the transition from rest to work on an average — 0.8 (range — 14 + 13) ml, or 0 4 per cent of the resting value The decrease was slightly more pronounced for men than for women, though the difference was not significant for the group ($p < 0.8$) nor for the different sexes.

In cases where two determinations could be made during work at different loads, no significant difference was obtained. The difference from resting value was insignificant ($p >$ 0 9)

The relationship between stroke volume/blood volume and heart rate (Fig 25) varied within normal range in both groups To diminish the random variation of the stroke volume due to biological variation a mean

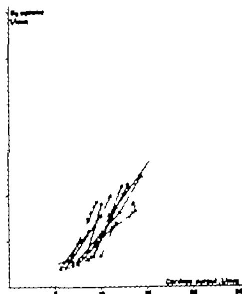


Fig 24 O yg n pt ke l STPD/min. i relation t cardi outp t l/min. t rest and d ri g w rk. Symbol in *Fig.* 21

fibrosis.

Blood vol., l	Blood vol. ml/kg	Pulse rate standing, beats/min	W_{170} sitting, kpm/min	Highest load in sitting position				Orthostatic test Pulse rate at work		
				kpm/min	Duration min	Pulse rate beats/min	Resp. rate breaths/min	Load kpm/min	Sitting, beats/min	Supine beats/min
7.6	83.4	80	1430	1500	6	176	27	1200	143	138
4.1	73.2	140	330	400	6	184	28	400	184	144
6.4	78.0	86	800	900	3	169	36	600	144	132
5.5	66.3	80	790	900	3	174	>36	600	143	142
3.0	82.4	126	700	900	6	188	40	600	160	134
4.1	82.1	100	560	600	2	154	33	400	146	132
3.1	83.6	108	350	400	4	178	40	200	132	116
3.8	67.9	82	560	600	6	176	30	400	147	134
4.1	63.1	120	700	600	3	168	36	400	147	144
4.4	69.8	132	350	400	6	175	41	200	153	137
5.3	81.5	110	630	900	5	187	48	600	166	154
4.5	83.3	108	350	600	2	164	30	400	132	118
3.0	69.4	104	650	600	2	152	39	200	103	116
3.4	71.1	125	400	400	6	168	44	200	146	130
4.3	88.0	124	300	200	6	152	>50	100	133	119
3.13 4.3 5.6	80.25 71.1 88.0	121.3 110 126	508 300 700	600 200 900		173.8 152 188	45.5 40 50	375 100 600	151.3 133 166	134.3 119—154
4.43 3.8 5.1	71.60 62.1 —83.6	107.4 82 132	540 350 700	543 400—600		163.3 152 178	37.3 30 —41	314 200 400	140.3 103—133	128.1 116—144

ducted. W_{170} = working intensity at pulse rate of 170 beats/min. Mean values calculated for the 11 cases with

relation to THb (Table 2 Fig 16) was significantly low in two patients in group III a (Cases 39 40) Two cases (Cases 1 3) in group III b had slightly high, but none had significantly increased heart volume (34) There was no significant average difference in group III b from the values predicted from THb ($p < 0.8$)

ECG in group III was normal at rest both in supine and in upright position as well as during and after the work test.

ECG in group III b was at rest within the normal variation in all cases. One patient showed a somewhat pronounced and split P wave (Case 41) another a slight right axis deviation and a diphasic T wave in load CR_2 (Case 18)

In standing position the ECG showed slight ST and T-deviations of the *sympathicotonic type in six patients* three of whom (Cases 15 31 36) showed changes of grade 1 and three more cases (Cases 1 18, 41) of grade 2 in a classification earlier reported from this laboratory (38)

Table 4. Lung volumes, l BTPS oxygen uptake of each lung in per cent of total V... of pulmonary fibrosis.

Case no.	IRV	TV	ERV	VC		FRC		RV	
				Obs l	% of pred.	Obs l	% of pred.	Obs l	% of pred.
4 cases with slight fibrosis									
23	2.75	0.65	1.47	5.87	105	3.03	88	1.56	83
17	0.88	0.41	0.97	2.26	61	2.48	89	1.61	83
39	2.14	0.65	0.76	3.55	88	2.74	84	2.02	11
40	2.62	0.59	1.99	5.20	110	3.66	116	1.71	87
11 cases with moderate to marked fibrosis									
7	1.96	0.48	1.68	4.12	68	3.64	85	2.12	107
1	1.37	0.52	0.93	2.82	67	1.86	87	0.90	68
3	1.04	0.45	0.54	2.03	55	1.78	64	1.24	75
32	1.79	0.50	1.00	3.29	88	2.16	80	1.08	72
15	1.26	0.46	1.11	2.83	81	2.04	79	0.98	59
31	0.89	0.26	0.35	1.50	43	1.47	66	1.16	78
34	1.08	0.45	1.88	3.41	61	3.26	81	1.45	74
4	0.89	0.39	0.59	1.87	51	2.07	76	1.50	93
41	1.28	0.57	0.80	2.66	77	2.03	105	1.30	110
38	0.51	0.81	0.84	2.26	39	2.23	63	1.40	64
18	0.41	0.52	0.84	1.77	36	1.44	61	1.00	58
♂ M	0.950	0.565	1.335	2.890	51	2.748	68	1.496	78
Range	0.41—1.96	0.45—0.81	0.84—1.88	1.77—4.12	36—68	1.44—3.64	31—63	1.00—2.12	43—107
♀ M	1.217	0.450	0.780	2.429	69	1.913	79	1.163	79
Range	0.89—1.79	0.26—0.57	0.35—1.11	1.50—3.29	43—88	1.47—2.10	64—105	0.90—1.50	59—110

IRV = inspiratory reserve volume. TV = tidal volume. ERV = expiratory reserve volume. VC = vital capacity. ... nitrogen wash-out index. Mean values calculated for 11 cases with moderate to marked fibrosis.

serve volume was on an average 2.35 l (range 0.88—3.75), *tidal volume* 0.58 l (range 0.41—0.65), *expiratory reserve volume* 1.27 l (range 0.76—1.99). The corresponding volumes in group III b were IRV = 1.14 l (0.41—1.96), TV = 0.49 (0.26—0.81), ERV = 0.97 l (0.35—1.88). Three patients in group III b (Cases 4, 18, 31) showed systematically lower values than reported in normals (67).

Vital capacity (VC) was, in group III a 4.22 (range 2.26—5.87) l or 61—110 % of predicted normal value (30). In group III b VC was 2.60 (1.50—4.12) l or 36—68 % of predicted normal value in the males and 43—88 % in the females. The difference from predicted value was not significant in group III a ($p < 0.2$) but highly significant in group III b ($p < 0.001$***), in which the males showed values lower than the females ($p < 0.01$**).

Functional residual capacity (FRC) was on an average 3.00 (2.38—3.66) l,

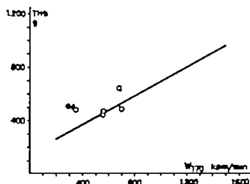


Fig 18 Tot l mou t f hemogl bin, g (r di t) l rel tion t W 7 kpm/min. (bs l sa) N rmal regres ion line nd ymbol l Fig. 16

estimate in a normal mat rial earlier reported from this laboratory (34) Four other patients in group III 1 h wed values above once standard err r of estimate (Cases 1 7 18) Two patients in group III a (Cases 39 40) and five in group III b (Cases 3 7 18, 34 38) showed alues above twice tandard error of estimate in the rela tion between W an l THI (Fig 18) The remaining two cases in group III a (Cases 17 22) n l three more pa tients in grou] III b (Cases 4 31 41) ha l values above once standard error of estimate

Working capacity in supine po i tion Two patients in group III a an l all but one in group III b (Case 41) had lower pulse rate during exercise in supine than in sitting position As a rule th heaviest work load in supine position was lower than in sitting position due to pain in the legs. Most patients were unable to perform work in supine position which increased the heart rate above 140 beats/min

Comparison between work in sitting and supine po ition In gr oup III a th lifference in heart rate during work at the same load in both po itions was 5.5 (range — 13 + 40) beats/min higher in sitting than in u[ine posi ti n

In grou] III 1 the corresponding values were 13 0 (range — 11 + 34) beats min The difference in per cent of] ulse level in sitting po iti n was 9 03 (range — 10 + 22 4) per cent B th differences were statistically sig nificant (p < 0 01**)

Using the approximately linear re lationship between rate of work and pulse rate the working intensity at] ulse 120 and 150 (W W) was calculated (40) For the whole group W averaged 102 kpm/min and W 178 kpm min higher in supine than in sitting p ition (Fig 19)

HEMODYNAMIC STUDIES

Right heart catheteri ati n wa per formed in all patients without com

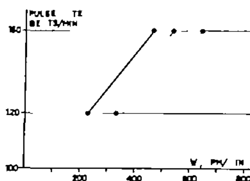


Fig 19 Pulse rat beat per min. (bscissa) in relation t rat f work, kpm/min. (or d tes) F ll line represents exercise i sit ting position, dotted li exercise i pine positio d ring heart thet rization nd broken line exercise i supine position.

Table 5 Alveolar ventilation diffusing capacity and related values in 15 sarcoidosis

Case no	Work load, kpm/min	Pulse rate beats/min	Respiratory rate breaths/min	$\dot{V}_E$ l BTPS/min	V_T l BTPS	$\dot{V}_{O_2}$ ml STPD/min	$\dot{V}_E$ l BTPS / $\dot{V}_{O_2}$ l STPD	RQ	Mechanical efficiency per cent	V_D ml BTPS	V_D/V_T	P_{aCO_2} mm Hg
4 cases with slight fibrosis												
22	Rest	56	9	7.55	0.84	277	27.2	0.76		227	0.28	38
	1200	149	20	76.02	3.60	2883	26.4	0.95	22.0	416	0.11	36
17	Rest	6	15	6.45	0.42	232	27.8	0.66		63	0.15	35
	300	141	24	2 10	1.12	1009	26.9	0.93	18.4	197	0.17	39
29	Rest	64	12	7.52	0.58	259	29.1	0.84		145	0.25	37
	600	148	16	40.77	2.55	1538	26.5	0.98	22.5	164	0.06	35
40	Rest	84	14	8.91	0.6	257	35.2	0.74		222	0.37	37
	600	162	29	65.16	2.25	1919	34.7	0.95	17.3	567	0.25	34
11 cases with moderate to marked fibrosis												
7	Rest		18	10.28	0.57	294	35.0	0.77		228	0.40	38
	600	140	26	41.51	1.60	1493	27.8	0.84	23.9	259	0.16	35
1	Rest	68	27	9.21	0.34	244	37.7	0.69		144	0.42	33
	400	142	24	34.41	1.43	1037	32.6	1.02	23.5	118	0.08	31
3	Rest	96	23	12. 4	0.53	365	34.9	0.83		165	0.30	33
	200	128	30	27.69	0.93	868	31.8	0.91	18.4	239	0.26	36
32	Rest	62	13	7.16	0.55	207	34.6	0.86		164	0.30	35
	250	111	19	18.77	0.99	691	27.2	0.85		108	0.11	32
	500	168	27	44.00	1.66	1340	32.9	1.02	20.7	308	0.19	34
15	Rest	92	17	6.27	0.37	246	25.6	0. 5		82	0.23	38
	400	126	29	39.43	1.36	1161	34.0	1.02	20.9	123	0.09	30
31	Rest	100	23	79	0.34	206	37.8	0.90		123	0.36	40
	200	152	31	26.60	0.86	687	40.2	1.02	14.1	254	0.30	45
34	Rest	58	18	9.58	0.53	231	41.5	0.94		258	0.49	45
	600	149	32	41.57	1.30	1624	25.6	0.93	20.6	363	0.28	46
4	Rest		20	8.70	0.44	231	37	0.83		147	0.33	34
	400	136	24	32.41	1.35	1072	30.2	0.93	22.7	246	0.18	34
41	Rest	64	17	8.46	0.50	256	33.0	0.76		159	0.32	33
	400	133	36	41.37	1.15	1247	33.2	0.83	19.0	282	0.25	30
36	Rest	90	13	9.61	0. 4	317	30.3	0.73		241	0.33	34
	200	122	30	32.88	1.10	938	35.1	0.75	15.5	442	0.40	31
18	Rest		15	9.93	0.66	219	45.4	0.67		305	0.46	45
	150	132	46	29.53	0.86	728	34.3	0.91	14.1	381	0.44	29
Rest M		8	18.5	9.068	0.505	59	35	0.811		183.3	0.357	38.2
range		58	13	6.27	0.34	206	25.6	0.69		63	0.22	33
		100	27	12. 4	0. 4	365	45.4	0.94		305	0.49	45
Work M	365	140		36. 56	1.226	1132.3	33.40	0.925	19.40	283.2	0.239	41.8
range	150	125	14	80	0.86	28	25.6	0.75	14.1	118	0.08	2
	600	168	46	44	1.66	1624	34.8	1.02	23.9	442	0.44	46

Symbols and abbreviations P 11 … l Federation Proc 9 602 1950 XL … excess lactate the 11 cases with moderate

of pulmonary fibrosis.

Strok. vol. ml	Lactic acid, ml l	Pyruvic acid, mF l	XI mF l	RA	RV		PA			PCV	BA			Pulm. vasc. resist. index.
				M	S	De	S	D	M	M	S	D	M	
114	1.22	0.000		2	25	8	23	12	17	11	124	78	100	1.34
148	1.83		0.23		46	6	48	18	32	15	146	83	106	1.39
133	2.33	0.173			33	3	42	13	26	13	134	79	104	1.84
50	1.33	0.060			31	6	31	10	20	8	104	71	83	3.30
	2.50	0.130	0.28		30	9	49	16	31	8	123	6	102	
77	4.50	0.213	0.94				48	8	23	13	125	79		1.59
90	1.1	0.115		1	21	7	17	9	12	8	103	62	84	1.07
117	1.78				34	10	29	17	23	15	124	65	87	1.30
121	2.72	0.200	0.69		40	10	30	16	22	13	121	62	84	1.12
88	0.83	0.083		5	20	2	20	9	12	2	103	69	87	2.12
	1.17				36	4	32	15	23	2	123	73	93	
106	2.22	0.190	0.36		29	4	37	17	26	2	134	76	100	2.31
					46	6	46	17	31	3	102	9	114	
98	0.78	0.073		2	17	1	16	7	11	2	109	64	83	1.34
97	1.00				23	1	23	9	14	6	129	71	89	1.92
109	1.89	0.123	0.39		25	−2	27	4	12	4	132	86	92	1.41
72	1.33			1	20	4	20	8	14	12				1.62
85	2.21				41	5	40	18	28	17				1.37
78	5.11				44	5	42	18	30	17				0.43
94	1.50	0.113		8	46	3	49	17	32	16	150	63	97	2.75
92	2.11	0.173	0.17		64	13	74	26	48	22	184	78	127	3.33
105	2.83	0.233	0.49		71	11	81	24	50	20	187	78	122	3.37
96	1.44	0.033		0	18	2	20	7	12	4	115	66	88	1.63
100	2.44				24	5	25	12	24	11	141	4	91	1.85
93	3.00	0.250	1.56		23	3	39	15	27	11	159	82	109	1.78
78	1.50	0.100		2	27	2	22	9	17	5	144	86	111	2.74
85	2.83				45	4	45	21	33	13	167	92	130	2.33
88	4.88	0.223	1.51		48	9	48	23	32	17	192	100	142	2.22
70	1.00	0.090		−4	31	−2	33	14	24	1	122	70	92	3.15
80	2.78	0.170	0.89		66	11	62	30	46	14	141	74	107	4.89
					68	14	67	22	50	4	167	93	119	
115	1.00	0.068		1.5	28	3	29	9	17	5	117	61	82	2.53
107	2.78	0.183	0.04		52	5	52	18	33	6	152	77	106	4.29
101	0.78	0.093		−1	23	1	22	6	13	1	113	60	78	2.31
87	1.83	0.133	0.86		43	5	40	14	26	8	147	69	103	2.89
79	2.22	0.220	1.42		44	3	44	14	27	6	167	72	105	2.17
93	1.00	0.093		−1	34	6	32	7	20	8	173	99	124	2.76
81	2.72				57	7	52	25	38	19	196	104	145	4.71
80	2.00	0.150	1.14		50	7	65	24	39	16	196	100	137	3.84
98				−3	28	2	25	8	17	3	118	78	97	3.50
89	3.00	0.183			64	7	68	28	50	16	153	104	128	4.51
66	2.22	0.160			36	−2	34	13	21	9	112	62	79	2.80
67	2.66	0.183	0.09		84	2	80	34	54	6	143	81	100	7.51

atrium, S = systolic, D = diastolic De = end diastolic, M = mean. Pulm. vasc. resist. index $\frac{\bar{P}_{P} - \bar{P}_{PCV}}{Q/m^2 \cdot m}$

Residual volume (RV) was 1.73 (1.56—2.02) l in group III a or 83—115 % of predicted normal value (39). In group III b RV was 1.28 (0.90—2.15) l, or 58—107 % of predicted value in the males and 59—110 % in the females. The difference from predicted value was statistically significant ($p < 0.01$**) for group III b.

Residual quotient RV/TC was 30.8 (24—42) or 80—138 % of the predicted normal value in group III a. The corresponding value in group III b was 33.7 (24—45) % or 116—142 % of predicted value in the males and 83—155 % in the females. The difference in group III b was probably significant ($p < 0.05$).

To summarize the lung volumes were decreased in two patients (Cases 17, 39) in group III a and more or less decreased in all patients in group III b. No patient showed a significantly increased absolute residual volume though the quotient RV/TC was significantly high in six patients (Cases 4, 7, 18, 31, 36, 39). Patients in group III b with moderate fibrosis on x-ray (Cases 7—15) did not significantly differ from those with marked fibrosis (Cases 31—18 ($p < 0.4$, > 0.05)).

Ventilation, alveolar gas exchange, pulmonary diffusing capacity, blood gas tensions and anaerobic metabolism were studied at rest in supine position and during exercise in sitting position (Table 5). The chosen work load increased heart rate to an average of 143 (range 128—168) beats/min. The respiratory quotient increased to an average of 0.94 (range 0. —1.02) during exercise. Oxygen uptake increased during exercise in group III a to an average of 1837 ml/min (range 1009—2883) corresponding to a mechanical efficiency (84, 92, 93) of 20.1 (range 17.3—22.5) %. In group III b oxygen uptake increased to an average of 1132 (range 728—1624) ml/min corresponding to a mechanical efficiency of 19.4 (range 14.1—23.9) %.

Ventilation. In group III a exercise increased respiratory rate to 22.3 (range 16—29) breaths/min, tidal volume to 57 (range 43—72) % of the vital capacity, minute ventilation to 48.3 (range 34— 0) % of the MVV. The *physiological dead space* and the relationship between dead space and tidal volume V_D/V_T was *significantly* high (2) during exercise in two patients (Cases 18, 30).

The arterial oxygen tension was slightly low (35) in group III a at rest in two patients (Cases 17, 40) but normal in all patients during exercise. In group III b the average value at rest was 65 (range 54—93) mm Hg and significantly low in four patients (Cases 3, 18, 36, 41). During exercise P_{O_2} was on an average 78.5 (range 46—115) mm Hg, significantly low in four patients (Cases 18, 34, 36, 41) and slightly low in another patient (Case 3).

Arterial carbon dioxide tension varied in group III a within normal limits both at rest and during exercise. In group III b the average value at rest was 36.2 (range 33—45) mm Hg and was significantly higher than usually found in normals (35) in two patients (Cases 31, 34) who also had high values during exercise when the group average of P_{CO_2} was 34.8 (range 29—46) mm Hg. One patient (Case 18)

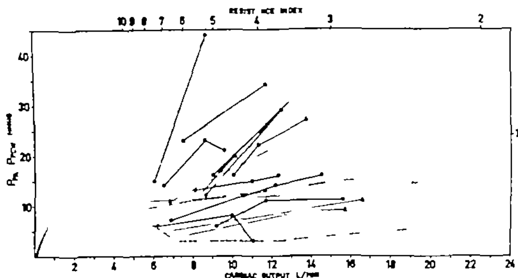


Fig. 20. Pressure gradient over pulmonary vascular bed, expressed as the difference between pulmonary arterial mean pressure ($\bar{P}_{PA}$) and pulmonary capillary venous pressure ($\bar{P}_{PCV}$) in mm Hg (ordinate) in relation to cardiac output, l/min, at rest and during exercise. Hatched area represents the normal range found in this laboratory. The oblique lines are isoresistance index lines. Triangles represent group III a, circles group III b. Filled symbols represent males and open symbols females.

the pulmonary valve were demonstrated.

PCV pressures. The mean pressure at rest was 7.3 (range 2—11) mm Hg in group III a and increased during work within normal limits.

The mean pressure at rest was 6.1 (range 1—16) mm Hg in group III b and increased during exercise to 11.2 (range 4—20) mm Hg. During exercise individual increases in PCV pressure of 11—13 mm Hg were observed (Cases 15, 31, 36, 41).

Two patients (Cases 1, 3) showed slightly high PCV pressures at rest. The pressures increased somewhat on the transition from rest to work, but did not increase further with increasing load.

The pulmonary vascular resistance

$$\frac{\bar{P}_{PA} - \bar{P}_{PCV}}{Qm/BSA} \text{ (Table 3)}$$

In group III a the resistance was on an average 2.20 (range 1.0 —3.30) at rest. Two patients showed slightly high values at rest, one of them (Case 17) decreased during work, of the others Case 40 showed a minor further increase. The remaining two patients showed unchanged values during work.

In group III b the resistance at rest was 2.84 (range 1.33—3.15) and increased during work to 3.40 (range 0.45—7.51). Seven patients (Cases 3, 4, 18, 31, 34, 36, 41) showed values higher than those earlier reported for

Diffusion capacity for carbon monoxide (Table 5 Fig. 28) was, in group III a at rest, 11 7 (range 7.8—17 ι) and increased during exercise to 27.3 (range 16 0—40.8) ml min/mm Hg or 83.3 (range 78—90) % of a value predicted from age and oxygen uptake (20) In group III b the corresponding values at rest were 9 6 (range 4.8—23 7) ml min/mm Hg and increased during exercise to 17.3 (range 9.2—32 1) ml/min/mm Hg, or 62 % of predicted value (range 28—88) In the entire group only two patients (Cases 7 22) at rest and one (Case 7) during exercise showed values within the normal limits earlier reported by Linderholm (48) and within once standard deviation from the predicted normal value (20) During exercise no patient in group III a but seven patients in group III b (Cases 3, 4 18 31 34 36, 41) showed values below twice standard deviation from the predicted value

D_{LCO} *m² BSA* was 6.0 in group III a (range 4.6—8 4) ml/min/mm Hg and increased during exercise to 14 0 (range 9.5—19 4) ml min/mm Hg or *in per cent of predicted* (20) *normal* value, 88.3 (range 81—94) % In group III b the corresponding values were 5.5 (2.9—11.6) ml min mm Hg at rest and during work 9 9 (range 6 1—16.8) ml min mm Hg or 70 (range 36—106) % of the predicted value During work no patient in group III a but seven patients in group III b (Cases 3, 4 18, 31 36 41) showed values lower than twice standard deviation from predicted normal value One more patient in group III a (Case 39) and one in group III b (Case ι) showed values lower than once SD

D_{LCO}*/l midcapacity* was in group III a at rest 3.6 (range 2 3—5.3) and increased during exercise to 8.3 (range 5 7—12 1) ml min mm Hg or 78.8 (range 65—85) % of the predicted normal value (20) In group III b the *corresponding values at rest were 3.8* (range 2.3—6 1) and during exercise 6 99 (range 4 4—11.5) ml/min/mm Hg or 81 (4ι—125) % of the predicted value

During exercise no patient in group III a, but two patients (Cases 34 36) *in group III b showed values* lower than twice SD from predicted value One more patient in group III a (Case 40) and four patients in group III b (Cases 4 7 36 41) showed values lower than once SD from the predicted normal value

To summarize, the diffusion studies showed that all but two patients (Cases 22) had low values. Seven patients (Cases 3 4 18 31 34 36 41) showed significantly impaired diffusion both absolutely and in relation to BSA. The changes were more pronounced in the patients with marked (Cases 31—18) than in those with moderate fibrosis of the lungs (Cases 7—15) ($p < 0.01$**) two of which (Cases 18, 34) showed significantly low values also in the relation to mid capacity of lungs.

Statistically the difference observed-predicted value during exercise in group III b was highly significant for D_{LCO} ($p < 0.001$ **) significant for D_{LCO}/m BSA ($p < 0.01$**) and probably significant for D_{LCO}/l mid capacity ($p < 0.05$*) The correspond

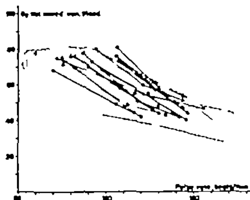


Fig. 21 Oxygen saturation of mixed venous blood, per cent, in relation to pulse rate, beat per min, at rest and during work. Normal range (Holmgren *et al.* 1960) is indicated by broken lines. Hatched area represent resting values. Filled symbols represent males and open symbols females. Triangles represent group III a, circles group III b.

all values for oxygen saturation fell within normal range (33 39). In group III b at rest eight patients had normal, two patients slightly low values and the test was omitted in one patient. During work four patients showed significantly low values (Cases 18, 31 34 36) and one a slightly low value (Case 41).

Mixed venous oxygen saturation ($S_{\bar{v}O_2}$) varied in group III a between 2—6 % at rest and 38—5 % during work.

In group III b $S_{\bar{v}O_2}$ *varied between* 68—81 % at rest and 40—57 % during work (Table 3). Two patients (Cases 18 41) showed slightly low values at rest, five other patients had tachycardia (Cases 3, 7 1 17 31) and $S_{\bar{v}O_2}$ was outside the normal variation with heart rate (Fig. 21). During exercise $S_{\bar{v}O_2}$ decreased with increased working intensity and heart rate all values fell during work within the normal range (11 39). Lowest observed value was 37.

AV-O₂ difference (AVD ml/l) at rest varied in group III a between 37—44 and in group III b between 31—4 ml/l, *i.e.* within the limits for normal variation (11 34 39). During exercise it increased with increasing working intensity, oxygen uptake and pulse rate to maximal values between 78—114 ml/l in group III a, and in group III b 60—96 ml/l. Plotted against oxygen uptake (Fig. 22) AVD varied within normal limits in all cases except Case 41 who had a slightly high value at the highest work load. In the relation to pulse rate three patients (Cases 3, 15 31) (Fig. 23) had lower values than normal at rest, one (Case 31) also at work. None had significantly high values.

Cardiac output at rest varied in group III a between 5.6 and 8.1 l/min and in group III b between 6.0 and 10.0 l/min. The corresponding values



Fig. 22 Arterio-venous oxygen difference, ml/l, in relation to oxygen uptake, l STPD/min, at rest and during work. Symbol as in Fig. 21.

Table 6 Mechanics of breathing in 15 sarcoidosis patients with signs of pulmonary

Case no	MVV free			MVV_{40}		MVV_{60} l min.	MVV_{80} l/min.	FVC		FEV	
	Obs l min.	% of pred.	Rate	Obs. l/min.	% of pred.			Obs. l	% of pred.	Obs. l	% of pred.
4 cases with slight fibrosis											
22	180	107	92	140	103	165	172	6 16	121	3.82	99
1	58	54	44	38	44	61	56	2.74	8	1.84	68
39	120	69	48	102	72	107	114	4 16	89	3 17	80
40	92	60	60	83	67	98	93	4.60	117	3 73	103
11 cases with moderate to marked fibrosis											
7	175	92	56	82	53	104	116	4 18	71	3.88	87
1	99	92	48	70	60	102	106	2.85	93	2.44	88
3	84	6	52	53	56	58	85	3.09	87	2.32	79
32	121	103	56	85	83	108	116	3 64	100	2.98	93
15	87	81	52		—		—	3.81	84	2.15	78
31	42	38	56	32	33	40	31	1.59	48	1 10	38
34	120	0	64	80	55	102	110	3.00	69	2.92	68
4	46	40	52	37	38	43	42	1 76	50	1.38	45
41	79	69	56	67	68	6	78	2.35	71	1 99	65
36	0	42	60	53	39	65		2.19	41	1.53	40
18	56	29	48					1.86	42	1.37	30
♂ M	107.8	58	57 0	72.7	49	90.3	113 0	2.955	58	2.425	56
Range	56—175	29 92	48—64	33—83	39—53	65 104	110—116	1.86—4 18	41—71	1.37 3 88	30 8
♀ M	9 7	71	53.3	57.3	60	71.3	73.0	2.584	76	2.051	69
Range	42 121	38 103	45—56	32 83	33—83	40 108	31 116	1.59 3.64	48—100	1 10—2.98	38 93

Maximum voluntary ventilation = MVV free $MVV_{40-60-80}$ breaths min. Forced vital capacity = FVC, forced
MMF maximum midinspiratory flow = MMIF forced inspiratory volume in one second = FIV . FIV In
moderate to marked fibrosis.

2.18 (range 1 10—3.88) l or 56 (range 30—87) of predicted value in the males, and 69 (range 38—93) % in the females. Six patients (Cases 4 18 31 34 36 41) had significantly low values. The values were slightly low in two others (Cases 3, 15).

Forced expiratory volum in one second (FEV %) in per cent f forced vital capacity in group III a was 1.5 (range 62—81) % or within normal limits (44). In group III b FEV averaged 9 1 (range 69—93) % r slightly low in Case 31.

Maximal Midexpiratory Flow (MMF) was, in group III a 2.76 (range 1 75—3.60) l sec or slightly low in Case 1. In group III b MMF was on an average 2.60 (range 0.68—7.21) and was significantly low in four patients (Cases 4 18, 31 36) and slightly low in four others (Cases 3, 15 34 41) (44).

Maximal Midinspiratory Flow

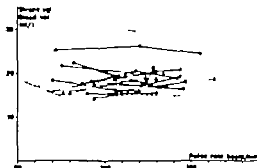


Fig 25. Strok vol me divided by blood o- l me ml/l, i relatio t pulse rat beats/ min, t rest nd d ri g w rk. Symbol i Fig. 21

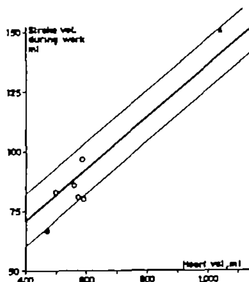


Fig 27 Stroke l m ml, determined i Fig. 23 in rel tion t heart ol me ml. Straight li es indic t orm l regression bet een these parameters ± tand rd erro f estimat

value for the stroke volume during exercise was calculated in each in dividual Plotting that mean value against THb in each case (Fig. 26) showed that one patient in group III a (Case 40) fell below twice another (Case 17) below once standard error of estimate for the normal material (39)

Three patients in group III b (Cases 18 36 41) showed values below twice two more patients (Cases 4 7) below once standard error of estimate

In the relation to heart volume (Fig 27) stroke volume during exercise in one pat ent (Case 36) fell below in another (Case 39) above twice stand ard error of estimate for the normal material (39) Five patients (Cases 1 3, 17 18, 31) had values lower than once standard error of estimate

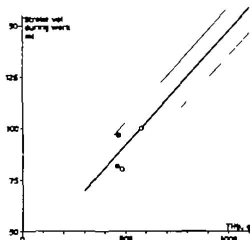


Fig 26 Mea l for ll observatio f troke ol me d ri g work i each subject, ml, i rel tion t tot l mou t of hemoglobin, g. Straight li es indic t norm l regres- io between these parameters (Holmgren *et al* 1960) ± st nd rd rror f estim t S m- bol in Fig. 21

PULMONARY FUNCTION

Static lung volumes The results of the determinations are presented in Table 4 In group III a the *inspiratory re*

height (24) in two patients (Cases 17 39) and slightly low in a third (Case 40). In group III b the corresponding values were 0.100 (range 0.037—0.221) l/cm H_2O in the males and 0.088 (range 0.039—0.162) l/cm H_2O in the females. In the above-mentioned relation to height seven patients showed significantly low values (Cases 3, 4, 7, 18, 31, 36, 41) and Case 15 a slightly low value. Compliance was also compared with a value predicted from observed vital capacity (24). In group III a, one patient (Case 40) had a significantly low and another a slightly low value (Case 39). In group III b only one patient had a significantly low value (Case 7) though three others (Cases 3, 18, 36) had somewhat low values also in comparison with a value predicted from vital capacity.

Total Lung Resistance (Table 6) during resting ventilation in group III a averaged 2.5 (range 1.84—3.80) cm H_2O/l/sec. or slightly higher than reported normal values (23, 24) in Cases 17 and 39. In group III b resistance was on an average 4.125 (range 1.55—6.68) cm H_2O/l/sec. in the males, and 4.049 (range 1.41—.91) in the females. Six patients (Cases 1, 3, 4, 18, 31, 36) showed markedly increased values.

Compliance and resistance during hyperventilation (values ± 1 SD). The tidal volume was 0.4 ± 0.11 l during resting ventilation, and increased during hyperventilation to 0.85 ± 0.24 l. The corresponding values for respiratory rate were 23 ± 4.0 and 22.4 ± 5.8 breaths per min. The pressure variations were 6.08 ± 1.3 cm H_2O increasing during hyperventilation to 11.38 ± 7.49 cm H_2O. The relation between compliance at resting and hyperventilation varied in the entire group within reported normal limits (24). The difference between the two values was insignificant ($p > 0.5$).

The corresponding relation for resistance was normal in all patients, the difference between the two values was probably significant ($p < 0.02$). The resistance increased during hyperventilation to significantly high values in two patients (Cases 17, 41).

To summarize, the values for maximal expiratory flow rates were significantly decreased in one patient in group III a (Case 17) who also showed a low compliance and a somewhat high resistance. In group III b four patients (Cases 4, 18, 31, 36) showed corresponding abnormalities. One patient in group III a (Case 39) and one in III b (Case 3) had low compliance and increased resistance as dominating findings, others had mainly decreased compliance (Cases 7, 40, 41) or expiratory flow (Case 34). One had, as the only finding, increased resistance (Case 1). One patient in group III a (Case 22) and two in group III b (Cases 15, 32) showed principally normal values for the mechanics of breathing.

The differences between observed and predicted values were for

MVV_{pre} and FEV: Group III a not significant ($p > 0.1$). Group III b significant ($p < 0.01$).

FEV % and MMF: Group III a probably significant ($p < 0.1$). Group III b not significant ($p > 0.1$).

Compliance height: Group III a not

trogen wash out time min and N_2 wash-out index in 15 sarcoidosis patients with signs

TC		RV/TC 100		N_2 wash out time min.	V_E (F N_2 = 2 %)/FRC	O_2 peak of total	
Obs., l	% of pred.	Obs %	% of pred.			Right lung	Left lung
7 43	100	21	81	5 0	7 7	33	47
3.87	65	42	127	3.8	10.5	—	—
5.57	80	36	135	2 8	7 9	54	46
6 92	104	24	80	2 8	7.6	55	45
6.25	77	34	142	3.6	8.5	49	31
3.72	80	24	83	3.1	8.4	50	30
3.27	59	38	123	3.2	8.6	54	46
4.37	82	23	93	1 9	6 6	50	30
3.79	71	25	81	2 8	12.5	48	32
2.66	52	44	147	3 2	10 4	73	27
4.06	64	30	115	4.2	11 0	54	46
3.37	64	43	155	2.3	9.1	58	42
2.96	66	32	119	1.8	9 5	57	43
3 66	46	38	136	1 4	11 4	59	41
2.77	42	36	138	2 7	17.0	59	41
4.383	57	34.3	133	3 00	11.98	53.2	44 8
2 77—6.25	42 77	30 38	115—142	1 4—4.2	8.5—17.0	49—59	41—51
3 801	71	33.3	114	2 61	9 30	53 7	44.3
2.66—4.37	52—86	24 43	83—155	1.8—3 2	6.6—12 5	48—73	27—52

FRC = functional residual capacity RV = residual olume TC = total lung capacity V_E (F — = 2%)/FRC =

or 83 to 116 % of predicted value in group III a In group III b FRC was 2.22 (1.57—3 66) l, or in per cent of predicted value 1—83 % in the males and 64—105 % in the females. The difference from predicted value (30) was not significant in group III a ($p > 0.4$) but significant in group III b ($p < 0.01$**) in which group th females had lower values than the men ($p < 0.05$) though the absolute mean value was lower for the males.

Total lung capacity (TC) in group III a a eraged 5 95 (range 3.87—7 43) l or 65—104 % of predicted normal value TC was, in group III b, 3.88 (2 66—6.25) l, or 42— 7 % of predicted value (30) in the males and 52—86 % in the females. The difference from predicted value was not ignificant in group III a ($p > 0.2$) but highly significant in group III b ($p < 0.001$***) in which the females had lower values than the males ($p < 0.02$*) although the absolute the mean value was lower in the males.

ales seemed to be equally distributed within the whole group the observed age difference might be accidental but the possible explanation could be a more rapid course in the males. One author (90) reports a higher frequency of lung fibrosis in males, though in his, as in Swedish materials the females dominate in the earlier stages (34)

In the present material circulatory studies showed that the dimensions of the cardiovascular system expressed as total amount of hemoglobin and heart volume were slightly but not significantly low (Table 2) none had an increased amount of hemoglobin (Figs 16 17) W_{70} sitting was significantly low in relation to THb (Fig. 18) in group III a ($p < 0.01$**) as well as in group III b ($p < 0.01$**). The difference between these groups was not significant ($p < 0.1$) nor did patients with marked fibrosis on x ray (Cases 31—18) differ from those (Cases — 15) with moderate fibrosis ($p < 0.2$). The males showed slightly lower values than the females ($p < 0.02$) In group III b five patients, however stopped working at a pulse level of 152—164 beats/min because of dyspnoea. In such patients the maximal working capacity (W_{max}) was taken to correspond to the highest working intensity they could maintain for at least four minutes (48) In the others the maximal working intensity was calculated from observed W and the maximum pulse level reported in normals of the same age (93). In all patients a predicted W_{max} was calculated from the total amount of hemoglobin. All patients who had a low observed W_{max} also had a low W value obtained by extrapolation. The difference from predicted value was for W_{max} highly significant for the whole group and for group III b ($p < 0.001$***)

The calculated W_{max} showed significant positive correlations to vital capacity ($r = 0.7$) compliance ($r = 0.73$) and D_{LCO}/m^2 BSA ($r = 0.74$) Pulse difference at work on the same load in sitting and supine positions (Fig. 19) was significant for the group ($p > 0.001$**) but the difference was not significantly correlated to W_{max} ($r = 0.26$)

In no case did the low working capacity in sitting position correspond to a significantly altered cardiac output in relation to oxygen uptake during exercise in supine position (Fig 24) The peripheral adaptation was normal during exercise judged as AVD or oxygen saturation in pulmonary blood (Figs. 21 22) except in one patient (Case 31) who showed normal values in relation to oxygen uptake, but a low AVD in relation to heart rate. Average stroke volume in group III a was low at rest and increased during exercise approaching normal values. In group III b the stroke volume at rest was slightly low and decreased insignificantly during work. Four patients (Cases 17 18, 30 41) had significantly low values in relation to THb during work, but only one of them had a low value in relation to heart volume (Figs 26 27)

Pulmonary artery pressures and the pulmonary vascular resistance during exercise were significantly increased

patients with signs of pulmonary fibrosis.

P_{aO_2}, mm Hg	$D_{L_{CO}}$ ml STPD/min mm Hg		$D_{L_{CO}}$ / m^2 BSA		$D_{L_{CO}}$ / l mid cap		$\dot{Q}_{sh}/\dot{Q}$	pH arts	Standard bicarbonate mE/l	Lactic acid, mE/l	Pyruvic acid, mE/l	XL, mE/l
	Obs.	% pred	Obs.	% pred	Obs.	% of pred.						
88	17.7	93	8.4	84	5.3	88	3.3	7.429	24	1.78	0.150	
82	40.8	90	19.4	88	12.1	83		7.337	19	6.22	0.215	3.67
70	7.8	62	4.6	71	2.8	61	4.7	7.437	23	1.83	0.170	
78	18.0	78	9.5	93	5.7	81		7.342	20	3.44	0.190	1.29
90	12.4	60	6.3	38	4.0	63	1.8	7.402	23	1.17	0.140	
88	26.7	80	13.6	81	8.7	84		7.316	19	3.28	0.210	1.53
70	9.0	67	4.7	67	2.3	48	3.2	7.400	23	1.22	0.093	
81	23.8	83	13.3	90	6.5	65		7.179	13	5.61	0.225	2.61
93	23.7	88	11.6	81	6.1	79	1.1	7.411	23	1.22	0.093	
103	23.1	82	15.7	79	8.2	71		7.264	20	2.23	0.133	0.60
86	9.8	74	5.9	66	4.8	102		7.449	23	3.72		
96	18.8	88	11.3	106	9.1	125		7.347	19	6.88		
66	7.3	43	4.2	48	3.6	64		7.453	23	2.44	0.183	
70	12.7	57	7.4	66	6.3	88		7.276	21	3.66	0.200	1.02
85	11.5	35	7.1	63	4.9	78	2.9	7.441	24	1.11	0.093	
93	18.4	72	11.4	86	7.8	100		7.417	21			
115	27.0	84	16.8	103	11.5	116		7.344	19	7.03	0.283	3.72
84	9.1	68	5.3	77	4.0	85	3.4	7.383	22	1.06	0.115	
94	17.7	79	10.4	93	7.8	103		7.351	18	5.16	0.170	3.60
73	4.8	32	2.9	38	2.8	56	4.1	7.427	24	2.17	0.183	
75	12.2	57	7.3	67	7.2	101		7.328	23	5.83	0.223	3.06
87	10.2	41	5.5	42	2.9	41	2.1	7.410	26	1.67	0.031	
57	21.6	56	11.7	60	8.2	54		7.261	16	7.19	0.170	1.54
78	11.9	66	7.4	79	5.2	91	3.4	7.430	22	0.94	0.075	
86	12.9	53	8.7	63	6.1	73		7.244	19	4.77	0.193	2.32
54	6.2	29	3.0	31	2.2	40	16.4	7.426	22	1.33	0.100	
62	11.6	41	6.6	46	5.0	56		7.359	18	5.22	0.238	1.82
82	6.1	31	3.0	29	2.3	38	13.8	7.397	21	1.39	0.165	
46	13.3	53	6.7	51	5.1	63		7.284	20	2.11	0.140	0.83
74	6.3	23	4.1	28	2.0	29	4.3	7.429	23	2.00	0.133	
60	9.2	28	6.1	36	4.4	47		7.371	18	4.11	0.183	1.81
76.8 34– 93	9.63 4.8– 23.7	60 23– 88	6.45 2.9– 11.6	53 28– 86	3.81 2.3– 6.1	65 28– 102	5.72 1.1– 16.4	7.424 7.283– 7.453	23.3 21– 26	1.732 0.94– 3.72	0.119 0.031– 0.183	
78.3 46– 115	17.30 9.2 32.1	62 28– 88	9.86 6.1– 16.8	70 36– 106	6.99 4.4– 11.5	81 47– 125		7.348 7.316– 7.384	19.0 16– 21	4.929 2.11– 7.10	0.194 0.125– 0.283	2.036 0.60– 3.72

$\dot{Q}_{sh}$ = blood flow through anatomical shunt, $\dot{Q}$ = total pulmonary blood flow. Mean values calculated for

resistance In the present material the total lung resistance was increased ($p < 0.001$***) especially in cases with marked fibrosis. It is striking that values for FEV % were quite normal even in cases with markedly increased total lung resistance

Compliance was, in relation to height, significantly reduced in group III b and there the difference between cases with moderate and marked fibrosis was not significant ($p > 0.5$) The difference between the sexes was not pronounced ($p < 0.1$) and all statistical differences were insignificant if compliance was related to vital capacity (24) Several patients with marked fibrosis had low values though a few had significantly decreased values. In a recent paper (75) 11 patients who were treated with steroids are reported Increase in lung volumes was not accompanied by a corresponding increase in compliance or in diffusion capacity

Distribution of inspired gas tested with nitrogen wash-out curves was usually normal but was somewhat impaired in four patients, two of whom (Cases 18 30) also showed an increased *dead space ventilation* and *decrease of P_{aO_2} during exercise* when P_{CO_2} was normal or slightly decreased Both patients had decreased diffusion capacities, and Case 30 also had elevated intrapulmonary venous shunt at rest Two patients (Cases 31 34) showed an increased P_{CO_2} at work thus indicating a slight alveolar hypoventilation an ther (Case 41) had a low P_{aO_2} as a s gn f ventilation perfusion listurban e \ pa tient, however had s gns f permanent alveolar hypoventilation judged as normal pH and standard bicarbonate values at rest Single patients showed slightly increased lactic acid values during exercise but the anaerobic metabolism was mainly normal

The gross ventilatory efficiency expressed as the conductance of the airways for oxygen (48 49) during work showed values slightly lower in five patients (Cases 3, 17 18, 31 36) than those calculated from normal data in the literature (48)

The diffusion studies revealed that all patients but two (Cases 7 22) had decreased values (Table 5) ($p < 0.001$***) In relation to their lung midcapacities (20) only two patients (Cases 18 34) had significantly low and five (Cases 4 7 30 40 41) slightly low values during exercise ($p < 0.05$) The males had lower values than the females ($p < 0.05$) and the patients with marked fibrosis on x ray differed from the others in group III b ($p < 0.01$**) judged as D_{LCO}/m^2 BSA. There seemed to be a co-variation between the impairment of diffusion and decrease in lung volume but the reduction in diffusing capacity does not appear to be solely related to the decrease in lung volume

During exercise there was a slight co-variation between diffusing capacity and pulmonary vascular resistance The disease may cause a decrease of the pulmonary capillary bed (27 64) which might contribute not only to the increased pulmonary vascular resistance but also to the decrease in diffus n capacity

In some cases it seems possible that diffusion could be a fact r limit

had a slightly low value during work and also ha l a low P_{aO_2} and a slightly low standard l icarbonate Case 31 ha l normal values f r P_{aO_2} an l stand ard bicarbonate Case 34 a low P_{aO_2} an l standard l icarbonate value

Acid-bas balance (Table 5) The pH and standard bicarbonate varied in group III a within the normal limits at rest l ut during exercise both le- creased in one patient (Case 40) due t an increase in lactic aci l

In group III b pH at rest wa 7 424 (range 7 38— 45) or within the nor mal range f variatk n During ex ercise the pH lecreased t an average f 7.348 (rang .21— 38) r igni ficantly l w in the al ve-mentioned Case 34 Standard l icarbonate wa 23 3 at rest (range 21—26) an l le creased during w rk to 19 0 (16—21) mEl

Ana robic m etaboli m The lactic acid concentration in grou III a at rest was 1.50 (1 1 —1.83) mEl an l increased luring exercise t 4 04 (3.28 —5.22) mEl All values a well as the correspon ling findings for pyruvi acid and e ces lactate varied within the normal range of variation in the literature and from thi laboratory (5 37 42) In group III b lactate con centration was 1 3 at rest (range 0.94—3 72) mEl Two patients (Case 1 34) showed lightly high values in relation to working intensity and pulse rate luring exercise In all pa tients the values for pyruvic aci l an l e cess lactate varied w thin normal limits.

Venou admixture (6, 7 10 3) to arterial blood due to an "anatomical shunt was slightly high in one pa-

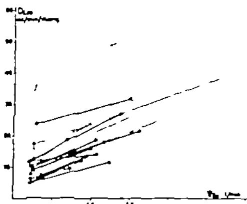


Fig. 21 Pulmona ry diffusion capacity f arbon mono id D_{LCO} ml STPD ml mm Hg i rel tion t ygen pt ke ($\dot{V}_{O_2}$) ml STPD min. t rest l plus nd during ex ercise in itting positio Normal elation f thi l bor tory indicated by broken lines. Tria gles represe t group III a, ircles group III b. Filled ymbol represe t m les nd open ymbol fem les

tient in grou III a (Case 1) and significantly high in two patients in group III b (Cases 36 41) The test wa omitted in two patients.

To summarize the ventilatory stu l ies in two patients (Cases 18, 36) showed an increased dead pace venti lation, n rmal or low P_{CO_2} and a low P_{aO_2} Case 18 als howed an increased ventilatory equivalent and the minute ventilation during exercise was 1 % of the MVV. Case 31 showed a slightly increased dead space ventila tion during exercise and a significant ly high P_{CO_2} but a normal P_{aO_2} (low oxygen saturation in arterial blood was observed during exercise at heart catheterization) Two m re patients (Cases 34 41) had signs of alveolar hypoventilation, ventilation-perfusion an l or liffusion disturbances.

ing difference D_{LCO} m² BSA, was not significant in group III a The dif ference between group III a and III b was not statistically significant ($p <$ 0.2) The male had systematically lower values than the females The difference was statistically probably significant ($p < 0.0$)

Broncho piromctry (12) The bronchospirometric data are presented in Table 4 as the V_{O_2} of each lung in per cent of total The V_{O_2} of the right lung was in group III a on an average 54 (33—5) % values within the normal limits reported in a study with the same technique (79) The investigation was omitted in one patient (Case 17) In group III b the V_{O_2} of the right lung was on an average 53.3 (range 40—59) % in the men and 55 (range 48— 3) % in the women One patient had a significantly low value of the left lung (Case 31) This patient showed a shrinkage of the left upper lobe on x ray (Fig 10 b) Three more patients who had pronounced fibrotic lesions on x-ray (Cases 4 18, 30) showed slightly low values of the left lung.

Distribution of inspired ga (Table 4) Nitrogen wash-out time (13, 52) in group III a averaged 3.6 (range 2.8—5 0) minutes. One patient (Case 22) had a somewhat high value but the wash-out index was normal In group III b the corresponding value was 3.0 (1 4—4.3) min. in the men and 2.61 (range 1.8—3.2) min in the females. One patient (Case 34) had lightly high value and also had a somewhat increased wash-out ndex (9)

Nitrogen wash-out index in group III a averaged 7.93 (range 7.6—10.5) all values within normal limits

In group III b the wash-out index averaged 11.98 (range 8.5—17 0) in the men and 9.30 (range 6 6—12.5) in the females. Three patients (Cases 15 34 36) had slightly high, one (Case 18) a markedly increased value

Maximum Voluntary Ventilation (MVV) (Table 6) was determined at a free respiratory rate and at three fixed rates, 40 60 and 80 breaths min. In group III a MVV_{free} wa on an average 112.8 (58—180) l min. or 54—10 % of predicted normal value (44) MVV_{40} averaged 90.8 (range 38 —140) l min In two patients (Cases 1 40) both values were significantly low

In group III b MVV_{free} was on an average 89 9 (range 42—1 5) l min or in the males 58 (range 29—92) % of predicted normal value and in the females 1 (38—103) % of predicted value MVV_{40} averaged 62 4 (range 32 —85) l min Four patients (Cases 4 18, 31 36) showed significantly low values for MVV One patient in group III a and four in group III b had slightly low values The tests MVV_{40-80} were omitted in two patients. The average values for $MVV_{40-60-80}$ increased with increasing respiratory rate MVV_{free} with respiratory rates between 44 and 9? breaths/min was higher than MVV_{80}.

Forced expiratory volume in one econd (FEV) averaged 3 14 (1.84—3.82) l or 88 (68—105) % of predicted normal value in group III a (44) One patient (Case 17) had a significantly low value In group III b, FEV was

show that pulmonary function in sarcoidosis may be impaired in various ways. In some few patients with bilateral hilar lymph nodes but radiographically normal lungs, normal functional data are usually reported (5, 33). In cases with lung lesions on x-ray restrictive ventilatory impairment with reduced lung volumes (4), hyperventilation, both at rest and during work, normal distribution, normal or impaired diffusion are generally described (1, 25, 26, 30). Other authors report significant elevation of the residual volumes, spirographic evidence of airway obstruction and impaired distribution (5, 33). Reports on cardiovascular function studies in sarcoidosis are few. One author (3a) reports normal findings or isolated diffusional impairment in ten cases without augmented fibrosis, but all types of functional disturbances and increased cardiac output in patients with lung fibrosis. Other authors (26) found mild pulmonary arterial hypertension in seemingly non-fibrotic cases, more pronounced in patients with fibrosis of lungs. The stage of the disease is, however, not usually stressed by the authors, and clinical data presented often do not allow an adequate definition of the actual stage at the time of investigation. The validity of a classification according to the duration of the disease is limited by the tendency to a silent debut and the great variation in the course of the disease.

The present material consists of 37 patients in whom the diagnosis was supported by lymph node biopsies. All available earlier information on lung x-rays were checked. On the basis of the clinical and roentgenological evaluation the chosen material was divided into the above mentioned three groups.

Group I. Eleven patients, 5 men and 6 women, with bilateral hilar lymph nodes but radiographically normal lungs.

Group II. Eleven patients, 5 men and 6 women, with sarcoidotic lung lesions but without signs of fibrosis on x-ray.

Group III. Fifteen patients with lung fibrosis of different degree.

Subgroup III a. Three men and one woman had minor and during recent years constant lesions on x-ray.

Subgroup III b. Eleven patients, four men and seven women with moderate to marked fibrosis on x-ray.

The physiological investigation was planned to allow an analysis of the pulmonary and cardiovascular dimensions and functions. Significant cardio-respiratory parameters were studied both at rest and during exercise in order to investigate whether the disease seemed to limit the transport capacity of oxygen.

The statistical significances (31) of the differences from normal values for some representative tests in groups I, II and III b and for sexes in general are demonstrated in Table 1. The individual variations are great, especially in group III b where some patients only showed slight functional disturbances but the major part of the group had severe functional impairment.

In *group I* the principal functional

fibrous.

FEV % Obs. %	FEV % of pred.	MMF Obs. l	MMF % of pred.	MMIF l/sec	FIV_1 l	FIV %	Compliance l BTPS/cm H_2O	Compliance % of pred. from height	Compliance % pred. from VC	Resistance cm H_2O/l BTPS/sec
82	81	2.51	70	7.70	6.00	97	0.372	148	133	2.05
67	83	1.75	63	3.32	2.52	92	0.084	41	99	3.31
76	99	3.16	83	7.42	4.16	100	0.107	50	70	3.80
81	107	3.60	105	4.99	4.53	91	0.104	33	43	1.84
93	113	7.21	160	3.73	3.38	88	0.096	36	52	2.71
86	106	4.47	137	2.73	2.42	83	0.152	102	133	4.48
73	91	1.84	39	2.74	2.41	78	0.039	20	53	6.23
82	96	3.38	91	2.81	3.09	83	0.138	80	99	2.42
77	93	1.86	83	2.61	2.37	84	0.116	64	101	1.41
69	84	0.68	22	2.06	1.26	80	0.045	27	100	7.91
81	103	3.13	73	6.19	3.22	89	0.221	93	131	1.55
78	93	1.28	28	2.51	1.63	94	0.050	28	78	6.61
85	101	2.48	74	4.18	2.51	93	0.077	50	73	2.66
70	91	1.12	31	3.06	2.14	96	0.044	16	52	5.84
74	91	1.16	23	2.91	1.86	100	0.037	23	63	6.68
78.5	100	3.153	72	3.978	2.700	93.3	0.100	43	80	4.123
70—93	91 113	1.12—7.21	23 160	2.91 6.19	1.86 3.88	88 100	0.037 0.221	16 93	52 131	1.55—6.68
78.9	97	2.284	72	2.800	2.244	85.9	0.088	53	97	4.349
69 86	84 106	0.68 4.47	22 137	2.06 4.18	1.26 3.09	78 95	0.039 0.152	20—102	53 133	1.41 7.91

expiratory olume in one second, = FEV_1 FEV 1 percent of FVC = FEV % maximum midexpiratory flow per cent of FVC = FIV Volumes in l BTPS time in seconds. Mean alues calculated for the 11 cases with

(MMIF) in group III a averaged 5.88 (range 3 32—7 70) l/sec and in group III b 3.23 (range 2 06—6 10) l/sec The difference between MMIF and MMF for the entire group was probably significant ($p < 0.5$)

Forced Inspiratory Volume in one second (FIV) in group III a averaged 4.3 (range 2.5—6.0) l or expressed as FIV % in per cent of forced vital capacity 95 (91—100) %

In group III b, FIV averaged 88.5 (range 78—100) % The difference between FIV % and FEV was highly significant ($p < 0.001$***) for the entire group The relation FEV FIV was slightly lower than reported in normals (24) in four patients (Cases 17 18, 2., 30)

Compliance (Table 6) during resting ventilation in group III a was on an average 0 167 (range 0 084—0 372) l/cm H O or significantly low in relation to a normal value predicted from

pacity Two cases had increased total lung resistance and, as a probable sign of an elevated airway resistance, low maximum midexpiratory flow values, and low compliance

(5) The alveolar ventilation was normal except for hyperventilation both at rest and during exercise in *two patients*.

(6) A low diffusion capacity absolute, in relation to body surface area and to the midcapacity of lungs. The decrease in $D_{I\,CO}$/l midcapacity was not statistically significant, however The cardiovascular function at rest and during exercise in supine position studied with right heart catheterization was normal in all cases except for a somewhat low stroke volume at rest approaching normal values during exercise The oxygen transport capacity during exercise was obviously limited by circulatory factors The lower capacity for work in sitting position might be explained by an increased effect of gravitational shifts of the blood seemingly due to lower venous tone

In *group II* (Table 1 Figs 1—4) the functional disturbances were mainly the same as in group I, though some cases showed a more marked impairment, disturbances in distribution and in ventilation perfusion relationships. Statistically no significant differences between groups I and II could be shown but the orthostatic reactions were more pronounced, the decline in maximum voluntary ventilation and in compliance was more marked, highly significant also in relation to the reduced vital capacity

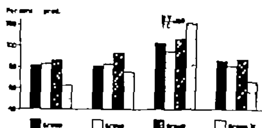


Fig 1 Lu g l mes l per cent f predicted orm l al s (11) Mea l es for the differe t groups
VC= ital pacity FRC=f ncti nal residual capa ity TC=t tal capacity

Two patients showed a somewhat impaired distribution of inspired air slightly high dead space ventilation during exercise, a somewhat low P_{aO_2} but normal I_{CO_2} Two patients had slightly high total lung resistance a low compliance and slightly decreased maximal midexpiratory flow Cardiovascular function during exercise did not significantly differ from normals but four cases showed a slightly high pulmonary vascular resistance Oxygen transport capacity during exercise was mainly limited by circulatory factors but in some cases diffusion capacity as judged from alveolo-capillary pressure gradient during exercise might be a possible limiting factor

In *group III b* (Table 1 Figs 1—4) several patients had marked to severe functional disturbances but others showed only minor alterations. The averaged values for working capacity lung volumes, maximal air flow and diffusing capacity were markedly lower than in group II but statistically the differences were significant only for VC ($p < 0.05$) TC ($p < 0.01$**)

significant ($p > 0.4$). Group III b highly significant ($p < 0.001$***)

Compliance Vit Cap. Group III a not significant ($p < 0$) Group III b not significant ($p < 0.5$)

Resistance in comparison with normals (24). Group III highly significant ($p < 0.001$***)

For $MVV_{(ind)}$ there was no significant difference between group III a and III b ($p > 0.1$) but a significant difference between cases with moderate (Cases —1) and marked (31—18) fibrosis ($p < 0.01$**). There was no statistical difference between the sexes ($p < 0.1$). Corresponding significance could be shown for $FEV_{1.0}$

No significant differences were shown for the compliance values between group III a and III b ($p > 0.4$) between patients with moderate and marked fibrosis ($p > 0.5$) nor between the sexes ($p < 0.3$)

Discussion

When pulmonary sarcoidosis progresses, interstitial and/or peribronchiolar fibrosis develops (50, 71, 7 81, 82). Studies of such patients have usually revealed a reduction of lung volumes and impairment of diffusion (3, 8, 61, 88). Marked peribronchiolar fibrosis could be the explanation of symptoms of airway obstruction found in some patients (17, 62, 78)

In the present study 1 patients with fibrosis of varying degree on lung x-ray were studied with the aim of investigating the types of functional disturbance and to analyse to what degree the disease seems to limit the oxygen uptake and transport capacity.

The group consists of seven men and eight women arranged in Table 1 according to degree of fibrosis on x-ray. The reason for admittance was in twelve cases subjective symptoms such as thoracic pains and effort dyspnoea. Some patients had periods of bronchitis and then dyspnoea also at rest. In most patients x-ray control 1959—61 were unchanged, one patient was somewhat improved (Case) others became successively worse, one patient died in cardiopulmonary insufficiency in July 1950 (Case 18). Autopsy revealed thickened pleural surface and massive fibrosis of the lungs, which microscopically showed sarcoid-lesions of all stages, obliterating panvasculitis and partly massive partly fine spidery fibrosis. Alveoli and bronchioles were dilated in extremely fibrotic parts of the lungs, and bronchiectasis and some real cavities were present in other parts of the lungs (1, 30, 60). The right heart showed moderate myocardial thickening, and an enormous dilatation of the right ventricle, a microscopically normal myocard and a moderate sclerosis in the pulmonary artery.

The material was divided into two groups (Table 1). Group III a consist of three males and one female, group III b of four males and seven females. The patients in group III a differ clinically from those in group III b. They had slight and in recent years constant lesions on x-ray. Mean age in group III a was 48 years (range 41—53) and in group III b in the males 34.5 years (range 29—44) and the females 4 .9 years (range 40—53). Males and fem

heart failure at rest or during exercise. A decreased stroke volume could in some cases alone or in combination with a slightly impaired gross ventilatory efficiency and/or diffusional disturbances with high alveolo-capillary pressure gradients during exercise limit the oxygen transport capacity.

In *group III a* various functional patterns were found. One of these four patients had quite normal cardio-pulmonary dimensions and function. Another had normal lung volumes and respiratory function except for a slight decrease of compliance, maximal voluntary ventilation and diffusion capacity but showed a significantly high pulmonary vascular resistance. The two remaining patients showed the same functional pattern as the patients in group III b with moderate lung fibrosis but had only slightly low diffusion capacity and normal pulmonary vascular resistance.

Some co-variations between function tests were found within the groups. In group I the orthostatic pulse difference at work in two positions was slightly (r = 0.67) correlated to decrease in D_{LCO}/sq.m BSA. In group II the decrease in vital capacity was significantly correlated (r = 0.79**) to decrease in compliance height. No close correlations could be shown in these groups, however between working capacity and circulatory dimensions, lung volumes, compliance diffusion and orthostatic *pulse differences* (The last named showed a slight but insignificant correlation (r = 0.564) in group II.)

In *group III b* the decrease in W_{m}

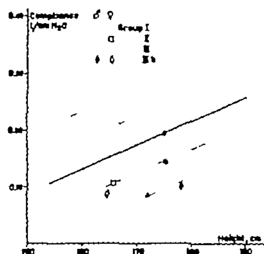


Fig. 3. Compliance l BTPS/cm H_2O (ordinate) in relation to body height, cm, (abscissa). Mean ± 1 es for the different groups. Straight line represent normal regression line described by Ehrner 1960 (8). Broken lines indicate normal mean value ± standard error of estimate and twice standard error of estimate.

was slightly to significantly correlated to decrease in vital capacity (r = 0.) compliance/height (r = 0.727) and D_{LCO}/sq.m BSA (r = 0.738**). The meaning of these correlations is uncertain in this small material, but obviously the co-variation is more pronounced in the group with moderate to marked fibrosis of lungs. The diffusing capacity showed during exercise a slight co-variation with pulmonary vascular resistance (Fig. 4). The disease may cause a decrease in pulmonary capillary bed (10, 27) with resulting decrease in capillary blood volume, decrease in diffusing capacity and increase of pulmonary vascular resistance.

Though the prevalence rate in the early stages is higher in females, it has been claimed (23, 36) that males

in one patient in group III a (Case 40) and in seven patients in group III b (Cases 3, 4 18 31 34 36 41) Four of these patients (Cases 18 31 34 36) had a moderately decreased arterial oxygen saturation during exercise No actual signs could be discerned however of right heart failure as indicated b the normal values for heart volume and the end diastolic pressures in the right ventricle and the normal increase in cardiac output during exercise in supine position None showed a markedly increased PCV mean pressure The tendency in patients in group III b t a slight decrease in stroke volume during work should however be noticed The stroke volume in the whole group is quantitativel related to the calculated maximal working capacity as in normal r in patient with mitral stenosi (11 36 39 49)

How far the increased resistance in pulmonary circulation in these patients with advanced pulm nary fibrosis was due to more or les diminished vascular bed (20 80 83, 80) or to alveolar hypoxemia (20, 66 68) was not further analysed One patient (Case 18) showed when oxygen wa inhaled luring exercise a slight decrease in pulm nary artery pressure *but still had an increased resistance*

Myocardial sarcoidosis can exist without causing symptoms (43, 53) In this group however ECG showed only insignificant changes, sympaticotonic deviations, or in three patients (Cases 7 31 36) premature beats during exercise

To summarize, the hemodynamic tudies showed pulmonary hypertension in several patients with different degree of fibrosis on x ray but no actual signs of right heart failure at rest or during exercise A decreased troke volume might in some cases, explain the low working capacity

Pulmonary function studies showed significantly reduced static lung volumes for the whole group Systematically the decrease in lung volumes was smaller in group III a than in III b and most pronounced in patients with marked fibrosi (Cases 31—18) though the differences were not statistically significant No patient had a significantly increased FRC. The decrease in vital capacity wa more pronounced in the males ($p < 0.01^{**}$) The decreases in FRC ($p < 0.05$) and TC ($p < 0.02^{*}$) were slightly more marked in the females. Maximal air flow judged as MVV and FEV was significantly reduced in the entire group ($p < 0.001^{***}$) without significant differences between the subgroups and sexes except that patients with marked fibrosis (Cases 31—18) had the most pronounced decrease ($p < 0.01^{**}$) The values for MMF and FEV % were not significantly decreased in the group nor individually for FEV %. Patients with a low FEV also had a low MMF The cor*relation to total lung resistance* was marked for both, but slightly more pronounced for MMF than for FEV . The first part of the expiratory flow has been shown to depend more on expiratory forces, the last part more on increase in airway resistance (41)

Total lung resistance in sarcoidosis has been shown (60) to increase due to both increased airway and tissue

pitalized patients with about the same degree of inactivity

Some patients in groups II and III b had slight signs of obstructive impairment of respiratory function to such a degree as might be expected from anatomically described (18, 34) peribronchial localization of sarcoidosis It seems unlikely however that ventilation impairment alone would limit the working capacity of these patients. The diffusing capacity was lowered to such a degree in some cases in group II and in several in group III b that it might, as judged from the increased alveolo-capillary gradients, be a possible limiting factor Some patients in group III showed somewhat low stroke volumes at work in supine position and also had increased pulmonary vascular resistance and more or less pronounced orthostatic reactions Myocardial sarcoidosis can exist without giving rise to symptoms (15) but in this material ECG showed only insignificant changes, sympaticocotonic deviations, or in some patients premature beats during exercise No actual signs of right heart failure could be shown The decreased stroke volume could in some cases partly explain the low working capacity

In patients with high total lung resistance or low compliance the distress due to laboured breathing might limit their working capacity Although not studied in detail, the work of breathing as judged from intrathoracic pressure variation during hyperventilation, generally did not seem to incapacitate these patients, but no certain conclusion can be drawn

It is obvious that the clinical picture and the functional disorders could vary with the stage of the disease The localization of the lesions is important peribronchiolar interstitial or perivascular predominance could give different functional disturbances such as obstructive or restrictive ventilatory impairment, alveolo-capillary block or increased pulmonary vascular resistance (18 32, 34) The resulting functional pattern may occasionally be specific but is usually complex or reflects some predominating disturbances

In the present material cases with bilateral hilar lymph nodes but without parenchymal lesions on lung x ray (Group I) and cases with parenchymal infiltrate but without signs of fibrosis (Group II) mainly showed slight restrictive ventilatory disturbances and somewhat impaired diffusion The cases in these two groups generally showed improvement on x ray during the post-examination period Single cases showed more or less pronounced disturbances of special functional parameters such as distribution or diffusion

In patients with lung fibrosis of different degrees single cases had normal function, but generally showed restrictive ventilatory impairment and various functional disorders increasing with increasing degree of lung fibrosis on x ray

In early stages stiffer granulomatous parts of the lungs may be separated by relatively normal tissue Probably most of the lung movements then occur in the more normal areas Often the granulomas are diffusely

ing oxygen transport capacity during exercise. The alveolo-capillary oxygen gradient ($P_{AO_2} - P_{aO_2}$) averaged in group III a 54.0 (range 4 —61) mm Hg during exercise and in group III b 56.0 (range 38—8) mm Hg. The patients were not examined during maximal work but the gradients were higher than those reported in normals (48) especially in five of the patient (Cases 4 18, 34 40 41).

Oxygen transport capacity during exercise could in this material be limited by various factors.

(1) Ventilation was in some cases slightly but not significantly impaired.

(2) The diffusion may be impaired to such a degree that, alone or in combination with slight ventilatory alterations, it might limit further oxygen uptake during exercise.

(3) Although not studied in detail the work of breathing as judged from intrathoracic pressure variations during hyperventilation did not generally seem to incapacitate these patients; no certain conclusions can be drawn however.

(4) A decreased stroke volume due to gravitational shift of the blood volume or possibly to increased vascular resistance could in some patients alone or in combination with a slightly impaired gross ventilatory efficiency and/or diffusional disturbances limit the oxygen transport capacity.

Summary

15 patients, 7 men and 8 women with various degrees of lung fibrosis were investigated with regard to cardiopulmonary function.

The circulatory dimensions were slightly low but did not significantly differ from what is found in normals.

Working capacity in sitting position was markedly lower than predicted from the circulatory dimensions. In supine position the pulse rate on a given load was lower than in sitting.

Static lung volumes and maximum voluntary ventilation were significantly reduced. None of the patients showed an increased residual volume. Compliance was low in 10 cases. Seven patients showed an increased total lung resistance three of them had almost normal values for maximal air flow normal or low compliance four patients with marked lung fibrosis all had significantly low compliance and maximal air flow judged as MVV FEV or MMF but essentially normal FEV %.

Distribution of inspired gas was normal except in four patients, two of whom had also an increased dead space ventilation and decrease of P_{aO_2} mal or slightly decreased. Two cases had increased P_{CO_2} at work but none had signs of permanent alveolar hypoventilation as judged from normal pH and standard bicarbonate values at rest.

Diffusion capacity was impaired in most cases, the decrease being less pronounced in relation to midcapacity of lungs.

The hemodynamic studies showed pulmonary hypertension in eight patients but no actual signs of right heart failure at rest or during exercise.

A decreased stroke volume could,

27. M \ ill R. S., Rankin, J nd F ral r R. E. Clin. Sci. 17 463, 1958.
28. Reid L and Lorriman G: Brit. J Dis. Chest, 54: 221, 1960
29. Reisne D Am. Rev Tub. 49 289 437 1944
30. Riley R. L., Riley M C. and Hill H Mc D., Bulletin J hns H pki Hosp. 31 345, 1952.
31. Snedeco G W Th low St t College Press, 1959
32. Spal D M A n. Intern. Med. 33 1141 1950.
33. St P J Schwartz A F ltman J A and Lovelock F J Am. J Med. 15 468, 1953
34. U hlinge E. Beit Klin. Tuberk. 114 17 1955
35. V ralraet J M. nd Gaensl E. A., J Franc. Med. et Chi Thorax. 8: 53, 1954.
36. W rm K Reind ll J nd Heilmeg L. Georg Thieme Verlag, 1958

GENERAL DISCUSSION

The aim of this study was to investigate the cardiopulmonary function in sarcoidosis with special reference to the different stages of the disease. The division of the material into groups was made according to the clinical course of intrathoracal sarcoidosis with hilar lymph node enlargement (Group I), more or less pronounced lung parenchymal lesions (Group II) and a chronic stage with fibrosis (Group III) (8, 19, 20). Microscopically the pure sarcoid lesions consist of epitheloid cellgranulomas. The lesions may be progressive, static or retrogressive. Healing appears to take place through hyalinization and fibrosis. The pathological basis of the radiological alterations of lungs has been supported by biopsy and autopsy (6, 18, 22, 28). In some few patients with bilaterial hilar lymph node enlargement but radiographically normal lungs, lung biopsy showed either normal picture or sarcoid granulomas of the same type as in patients with parenchymal infiltrates but without signs of fibrosis on x-ray. Lesions of the miliary type have clinically a great tendency to resorb (18, 21, 29) but may remain unchanged for years or progress to form coarse nodular infiltrations, coalesce into diffuse densities or recede. The occurrence of fibrosis contributes to these patterns and their variation (18).

The granulomas may occur anywhere in interstitial tissues. They show however a distinct tendency to cluster in regions of small lymphatic channels as in the peribronchial, perivascular and subpleural areas in the lungs (18, 34). Widespread involvement of tissues by uncomplicated sarcoid lesions is due primarily to numerical increase of the granulomas. Lesions in the interstitial tissues may distort the bronchioles, the vessels and alveoli but they rarely disrupt the lining epithelium. In later phases there may be fusions of the lesions into a mass of intermingled granulomatous elements and dense fibrous tissue. Instead of bronchostenosis through shrinkage, a dilation of the bronchi is sometimes observed (18). Extensive fibrosis of lungs is a common finding at autopsy. In most cases granulomatous lesions are still present alternating with dense fibrosis, spongy emphysematous and bronchiectatic areas. In an advanced stage there is often cor pulmonale (83). Myocardial, pericardial and even endocardial granulomas or fibrosis are sometimes found in different stages of the disease (15, 18).

Previous reports in the literature

a degree that it might be a possible limiting factor for further oxygen uptake during exercise Cardiovascular function did not significantly differ from normals but four patients showed a slightly high pulmonary vascular resistance during exercise

In *group III* several patients had marked to severe functional disturbances but others showed only minor alterations Principally they showed the same type of respiratory disturbances though more pronounced than in patients in the other groups. Lung volumes were markedly reduced, and no patient had significantly increased residual volume Compliance was low in ten patients. Seven had a high total lung resistance often increased to such a degree that it might possibly not only depend on an increase of tissue resistance or decrease of lung volume Though in some of these patients the correlation to decrease in maximal expiratory airflow was not clear an increased airway resistance seemed obvious. Gross ventilatory efficiency though somewhat impaired in some cases, usually did not seem to limit oxygen transport capacity alone but might strengthen the importance of observed diffusional disturbances with high alveolo-capillary pressure gradients. The hemodynamic studies showed pulmonary hypertension in eight patients but no actual signs of right heart failure at rest or during exercise A decreased stroke volume could in some patients alone or in combination with ventilatory and/or diffusional impairment limit oxygen transport capacity during exercise

Four patients in this group had only minor and during recent years constant fibrosis on x ray One of them showed quite normal cardiopulmonary function one had significant functional disturbances with increased pulmonary vascular resistance

The men in group III with moderate to marked fibrosis on x ray showed somewhat more pronounced functional disturbances The difference was not significant but should be noticed especially as the mean age was markedly lower for these men than for the females

The functional pattern in pulmonary sarcoidosis seems generally to be related to the stage of the disease but also in patients without visible lesions on x ray functional disturbances can be shown and the type and degree of impairment might vary with the localization of lesions both in earlier stages and in the fibrotic stage where the functional findings varied from normal to severely impaired In order to get as complete a view as possible of the sarcoidotic disease in a special patient it is, according to the present study necessary not only to perform a careful clinical evaluation, but also a thorough functional study

Table 1 Statistical significances of the differences from normal values In group I, II, III b and for the sexes in general. Men lues for orthostatic work test and for pulmonary scula resistance index higher than normal values, all other mea lues lower than predicted normal lues. THB = total amount of hemoglobin, W_{170} = orking intensity t pulse rate f 170 beats min. Wmax = observed or calculated ma imal working intensity VC = vital capacity FRC = functional residual paeity TC = total lung capacity MVV = maximal oluntary entilation, MMF = ma imal midexpiratory flow Co_{height}, Co_{VC} = compliance compared with alue predicted from either body height or tal capacity $D_{L_{CO}}$ m² BSA, $D_{L_{CO}}$ l midcap. = diffusion pacity of lungs for carbon monoxide as compared with body rface area or midcapacity of lungs Orthostatic work test = pulse difference t work on the same load in sitting nd supine position. Pulmonary vascular resistance index = $\frac{\bar{P} - \bar{P}_{PCV}}{Q\ m^2\ BSA}$

	Group I	Group II	Group III b	Men	Women	Sex difference
THb	<0 05	<0 1	<0 3	<0 01**	<0.3	<0.05
W_{170}	<0.01**	<0 0.	<0 01**	<0.001***	<0.001***	<0 02*
W_{max}	<0 01**	<0.1	<0 001***	<0 001***	<0 001***	<0.2
VC	<0.001***	<0 01**	<0 001***	<0 001***	<0 001***	<0.1
FRC	<0 1	<0 05	<0.01**	<0 001***	<0.05	<0.001***
TC	<0 001***	<0 001***	<0 001***	<0 001***	<0.001***	<0.1
MVV_{free}	<0 02*	<0 001***	<0 01**	<0.01**	<0 001***	<0 7
MMF	<0 02*	<0.3	<0.2	<0.2	<0 01**	<0.8
CO_{height}	<0 01**	<0 001***	<0 001***	<0 001***	<0.001***	<0 3
CO_{VC}	<0.05	<0 001***	<0.5	<0 01**	<0.05	<0 01**
$\frac{D_{L_{CO}}}{m^2 BSA}$ during work	<0 01**	<0 01**	<0.01**	<0 001***	<0 001***	<0.1
$\frac{D_{L_{CO}}}{l\ mid.\ cap}$ during rk	> 0 9	<0 1	<0 05	<0.01**	<0.2	<0.1
Orthostatic work test pulse difference sitting supine	<0 05	<0.001***	<0 01**	<0 01**	<0.001***	<0.5
Pulm. vasc resist. index at work	<0 2	<0.3	<0 001***	—	—	<0.7

disturbances were (Table 1 Figs. 1—4)

(1) Slightly low circulatory dimensions.

(2) *Significantly low working capacity* in sitting position

(3) A tendency to orthostatic reactions both at rest in standing position and during work in sitting as compared with supine position

(4) Significantly decreased lung volumes. Slightly low values for maximal expiratory air flow and maximal voluntary ventilation but significantly low compliance values in relation to body height and slightly low values also in relation to observed vital ca

and pulmonary vascular resistance ($p < 0.01$**)

The findings in group III b can be summarized as follows

(1) Slightly but insignificantly reduced circulatory dimensions.

(2) Markedly reduced working capacity in sitting position.

(3) Orthostatic reactions both at rest in standing position and during work in sitting as compared with supine position.

(4) Markedly reduced lung volumes, and maximal voluntary ventilation. None had an increased residual volume The significant decrease in compliance wa in relation to the reduced vital capacity le s pronounced and statistically not significant. Total lung resistance wa high in six patients two of whom had moderate signs of fibrosis on x ray an l normal values for maximal air flow normal or low compliance The remaining four patients showed marked fibrosis on x-ray and all had significantly low values for compliance and maximal air flow judged as MVV FEV or MMP but essentially normal FEV %

(5) Distribution of inspired ga was usually normal but somewhat impaired in four patients, two of whom also had an increased dea l space ventilation, decrease of P_{aO_2} during exercise while P_{CO_2} was normal or sligl tly decreased One of these and one further patient with corresponding alterations in blood gas tensions showed an increased venous ad mixture at rest during oxygen breath ing indicating an increased anatomical shunt Two cases showed an increased P_{aCO_2} at work but no patient had signs of permanent alveolar hypoventilation as judged by normal pH and standard bicarbonate values at rest

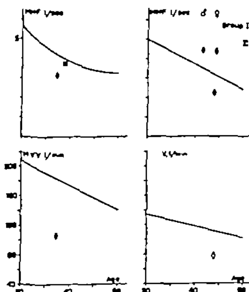


Fig 2. M lm l irflow (ordinat) i relation to ge (bscis) Mea lues f the differe t groups. Vol mes l liter BTPS. MMF l sec=maximal midexpiratory flow Straight line represent ormal regression line described by hj lmer *et al* (10) Broken line indic tes normal me value minu twice st ndard rror of estimat
MVV l ml =ma im l ol tary entil tion t free respiratory rate.
Straight line represent normal regres ion line described by Grimby *et al.* (11) Broken lines indicat normal mea val mi- us once tandard error f estimat and twice st nd rd rror f estimat

(6) Diffusion capacity was low in all but two patients the decrease was less pronounced but statistically probably significant also in relation to observed midcapacity of lungs.

(7) The hemodynamic studies showed pulmonary hypertension in seven patients but no actual signs of right

KUNGL. BOKTRYCKERIET P. A. [illegible]STEDT & SÖNER

might have a higher frequency of lung fibrosis. The functional differences between the sexes regardless of groups are small, however (Table 1) except for a more pronounced decrease of functional residual capacity and compliance in the relation to vital capacity in the males. The mean ages do not differ much in groups I and II but in group III b the males averaged 34.5 years (range 20—44) and the females 47.0 years (range 40—53) This dif ference might be accidental but the possible explanation could be a more rapid course in the males. The correlation between the findings on x ray and degree of functional impairment showed large variations and could not be statistically proved though case in group III b with marked lung fi brosis had much more pronounced functional impairment and partly dif fered significantly from the rest of group III b Single patients showed minor functional disturbances, though x ray showed incontrovertible signs of fibrosis, others marked functional impairment while lung x ray was al most normal

The reason for a limitation of the oxygen transport capacity could be circulatory respiratory or a combi nation of these factors. The main limitation in groups I and II was cir culatory as in normals. During heart catheterization in supine position nor mal values for stroke volume pressures, flow and peripheral adaptation were usually found during exercise The above mentioned orthostatic pulse reactions at rest and during work in sitting as compared with supine position and a significant increase in

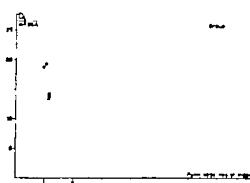


Fig 1 Pulmonary diff I g capacity for carbon mono ide ml STPD ml 'mm Hg per sq m. body surface area D_{LCO}/m² BSA, d ri g ercise I sitti g position (ordi t) i rel tion t pulmo ry scular resi t nce index, $\frac{\overline{P}_{PA} - \overline{P}_{PCV}}{Q\ m^2\ BSA}$ d ring ercise I pine position (bscis)

stroke volume on transition from rest to work also in supine position seemed to support an assumption that also in sitting position blood was pooled peripherally in a higher degree than in normals This might result in a decrease of the central blood volume and a decrease in stroke volume The observed tendency in these patients to orthostatic reactions is probably due to a venous tone lower than nor mal in upright position. In prelimi nary stud es (12) it has also been possible to eliminate the pulse difference with the aid of an inflated g suit during exercise in upright posi tion. Whether this is caused by the sarcoidosis or other factors cannot be decided at present. In preliminary studies (2) no corresponding orthostatism could be shown in other hos-

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spread in the affected tissues however. In later phases there may be localized fusions of the lesion but also in the fibrotic stage diffuse spl dery fibrosis can sometimes be observed. The respiratory tissue may be injured by infiltrates, compression or traction, or secondarily by damaged lymph sinuses or alveolar capillaries (18, 31).

It has been shown that total lung resistance in pulmonary sarcoidosis may increase owing partly to greater tissue resistance and partly to increased airway resistance (24) but a decrease in airway resistance was also observed. In the present material an attempt has been made to correlate the finding in mechanics of breathing and diffusion both to parameters for body height and for lung volumes. Those comparisons are limited, however by the fact that it was not possible to study the lung volumes simultaneously with the other tests. There seemed to be a certain co-variation between the reduced lung volumes and the impairment of compliance and diffusion in some cases in all groups, but usually there was an alteration of function also in relation to the decreased lung volumes. Observed increase in total lung resistance might in some cases with normal maximal air flow be due to increase in tissue resistance but especially in group III the total lung resistance was increased to such magnitude that an increased airway resistance seemed obvious, often without distinct correlation to decrease in maximal air flow and lung volumes.

References

1. *Baldwi* F D F *Cournand,* A and *Richards* D W Medici 28 1 201 1949
2. *Bergqvist* S and *Svanberg* N Unpublished observations.
3. *Brech* C A Anon Bet ro, Crone & Stratton, 1956.
4. *Brun* T and *Wassl* F Act Med. Scand. *104* 63 1940
5. *Coates* F O and *Comroe* J H J Clin. Invest. *30* 848, 1951
6. *Cagell* D B *Marks* A, *Ellicott* M F *Badger* T L and *Gaensl* E A The Amer Rev Tub 74 317 1956
7. *Donevan* R F *Palmer* W H *V* C J and *Bates* D V J Appl. Physiol. *14* 483, 1959
8. *Dressler* M Springer Verlag. 1942.
9. *Ehrn* L Act Med. Scand Suppl. 353. 1960
10. *Fowler* R E. Physiol. R 37 391 1957
11. *Cromby* C and *Söderholm* B. Personal communications, 1961
12. *Holmgr* A Unpublished observations.
13. *Holmgre* A *J* son B and *Sjöstrand* T. Acta Physiol scand. *49* 343, 1960
14. *Hyatt* R E, *Schilder* D P and *Fry* D L. J Appl. Physiol. *13* 331 1958.
15. *Kirchh* I R. Act Med. Scand. *168* 223, 1960.
16. *Kjellmer* I *Sandqvist* L and *Bevegård,* G. Personal communications.
17. *Lind holm* H Act Med. Scand. *163* 61 1959
18. *Longcope* W T and *F* *lman* D G Medicine *31* 1 1952.
19. *Löffl* W Helvet med. Acta, 4 747 1937
20. *Löffl* W and *B* *h* *ne* W J . Handbuch der I n. Med. 4 464 1956.
21. *Löfgre* S. Acta Med. Scand. *145* 424. 465, 1953.
22. *Löfgr* *n,* S. Personal communications.
23. *Löfgren* S and *Stavenow* S. Tra s. II I ternat. Congr Sarc Washington, 1960.
24. *Marshall,* R. and *Dubois,* A B Clin. Sci. *15* 473, 1956.
25. *Marshall* R *Smelli* H *Baylis,* S. H *Hoyl* C. and *Bates* D. V Thorax, *13* 48, 1958.
26. *McCl ment* J H R *nz* *tti* A D *Himmelstein* A and *Cournand* A Amer Rev Tub. 67 163, 1953.

GENERAL SUMMARY AND CONCLUSIONS

The cardio-pulmonary function was studied in 37 patients, who on the basis of clinical and roentgenological evaluation were divided into three groups.

Group I. Eleven patients, five men and 6 women, with bilateral hilar lymph node enlargement but radiographically normal lungs.

Group II. Eleven patients, 5 men and 6 women, with sarcoidotic lung lesions but without signs of fibrosis on x-ray.

Group III. Fifteen patients, 7 men and 8 women, with lung fibrosis of different degree.

The physiological investigation was planned to allow of analysis of the pulmonary and cardio-vascular dimensions and functions. Significant cardio-respiratory parameters were studied both at rest and during exercise in order to investigate whether the disease seemed to limit the transport capacity of oxygen.

The patients in *group I* were generally little incapacitated by their disease but their physical working capacity in sitting position was decreased. In supine position the pulse rate on a given load was generally lower than in sitting and also at rest in standing position these patients showed orthostatic reactions. Alveolar ventilation and alveolar gas exchange was normal in all patients but several showed decrease of lung volumes, a low compliance and a decreased diffusion capacity though these disturbances were not of such magnitude as to limit their oxygen transport capacity during exercise. The lower working capacity in sitting position could be explained by an increased effect of gravitational shifts of the blood seemingly due to lower venous tone. The disturbances in respiratory function were interpreted as indicating the presence of parenchymal infiltrations although not visible on x-ray. The cardiovascular function at rest and during exercise in supine position studied with right heart catheterization was normal in all cases except for a somewhat low stroke volume at rest approaching normal values during exercise.

In *group II* the functional disturbances were mainly the same as in group I though some cases showed a more marked impairment, and disturbances in distribution and in ventilation-perfusion relationships. The orthostatic reactions were more pronounced, and the decline in maximum voluntary ventilation and in compliance was more marked. Ventilation did not, however, usually limit their working capacity. In some cases diffusion capacity was decreased to such

ACKNOWLEDGEMENTS

This study, which was carried out during the years 1958—61, was made possible by co-operation between the Lung Clinic at St. Gorans Sjukhus, and the Department of Clinical Physiology at Karolinska Sjukhuset, where physicians and other personnel contributed generously to the work.

Docent Sven Löfgren, as head of the Lung Clinic, has had supervision over the patients, and, with his thorough knowledge of sarcoidosis has been of invaluable assistance to me.

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Nils Svanborg

CHAPTER I

METHODS

The bicycle ergometer

In this investigation two types of bicycle ergometers have been used. The first is an oil bicycle ergometer of the type described by Dahlström (1949) (3) which is only used in a minority of the tests, and the second is described by Holmgren and Mattsson (1954) (4) and Holmgren (1956) (5).

The latter type consists of a frame with a pedal mechanism similar to that of an ordinary bicycle but of a more stable construction. The load consists of an ordinary, separately magnetized d. c. generator. The transmission between the pedalling wheel and the generator is effected by means of a universal joint. The effect of the generator is transmitted to a resistance. The voltage of the generator is kept constant by the feed back of the difference in voltage between a reference voltage indicator and the generator voltage to an electronic amplifier which regulates the current to the field winding of the generator. This arrangement maintains a constant output from the generator at variations in the pedalling rate between 45 and 75 revolutions per minute. The rate is controlled with a speedometer.

The ergometer was calibrated by running a pendulum generator with a direct connection to the pedalling wheel of the ergometer, so that all losses were included in the measured effect. The accuracy of the ergometer is within ± 5 per cent at all loads between 200 and 2000 kpm/min.

The exercise test

The exercise test is always preceded by a routine clinical examination which generally includes the usual x-ray of heart and lung.

Before the test starts, the patient rests in a recumbent position for about twenty minutes and the [illegible] the pulse and respiratory [illegible] the Ecg are recorded. T[illegible] d only if the Ecg show[illegible] in progress.

The first stage is an orthostatic test, where pulse frequency and Ecg are recorded after standing erect for eight minutes. After this, the patient gets on the bicycle ergometer and a new Ecg is recorded before the exercise starts. For men, the first work load is usually 300 kpm/min and it is increased by 300 kpm/min each time if no pathological Ecg changes or symptoms are observed, and provided the patient makes no complaints and the pulse rate does not

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centration is calculated from analysis of alveolar air During the breathing of carbon monoxide the formation of carboxyhemoglobin is determined by Haldane's equation

$$\frac{[COHb]_B}{[O_2Hb]_B} = M \times \frac{pCO_B}{pO_B}$$

where M is a constant. The original calculations involved in the alveolar CO method [Sjöstrand 1948 (9 10)] have later been slightly modified to allow for the small losses of CO in the bags of the closed system [Sjöstrand 1955 (14) and introducing a slightly higher value for M 245 (Carlsten Holmgren Linroth Sjöstrand, Ström (1954) (12) cf also Wiklander (1956) (13) and Robbe (1959) (15) The method has been used extensively [Sjöstrand 1949 (16) and 1953 (11) Kjellberg Rudhe and Sjöstrand 1949 (17) Åstrand 1952 (18) Carlsten et al. 1954 (12) Fretheim 1953 (19) Hallberg 1955 (20) Norlander 1955 (21) Wiklander 1956 (13) Holmgren 1956 (5) Linroth 1957 (22) and Robbe 1959 (15)]

When used as a routine method for a material of this kind, the error involved calculated as the standard deviation for a single determination varied between 3 and 5 per cent.

Determination of hemoglobin concentration

The hemoglobin concentration in the blood was determined as oxyhemoglobin by spectrophotometry (1 part blood in 200 parts 0 1 per cent sodium carbonate solution) at 545 m with a Beckman B spectrophotometer

Roentgenological determination of heart volume

The heart volume was determined roentgenologically according to the method used by Larsson and Kjellberg (1948) (23) and modified by Kjellberg et al. (1949) (24) The subjects were investigated in a prone position. The calculation of the cardiac volume was made with the aid of two roentgenograms — one obtained with a lateral projection and the other with a posterior – anterior projection. The latter is obtained with the central ray angled 30 caudally to facilitate the determination of the lower contour of the heart The average error of a single determination is, according to Kjellberg et al. (1951) (25) about 4 per cent

The advantages in determining the roentgenological heart volume in a prone position have been discussed by Larsson and Kjellberg (1948) (23) They investigated the effect of orthostatic changes on the heart volume, and found that there was a decrease when changing from a lyin to a sitting position if at the same time, the pulse frequency increased to values above 80 beats per minute. The magnitude of this decrease was a function of

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CHAPTER II

ELECTROCARDIOGRAPHIC CHANGES DURING A COMBINED ORTHOSTATIC AND EXERCISE TEST IN A RANDOM SELECTION OF FORTY TWO HEALTHY MEN BETWEEN 35 AND 50 YEARS OF AGE

Introduction

The changes of the S—T and T intervals are important for the clinical interpretation of the exercise test and the differentiation between normal and abnormal S—T variations is often very difficult.

Experimental studies on the variability of the S—T and T intervals during work in 70 healthy individuals of both sexes have been published by Sjöstrand (1950) (8 9) He showed that the S—T interval varies with rising pulse rates according to a curved line. There was in some cases an elevation at low frequences. In all cases the S—T level was depressed at higher pulse frequencies and this was more pronounced the higher the frequency was. The S—T level was coincident with the isoelectric level (P—Q level) at a fixed pulse rate for each individual but varying between individuals.

The amplitude of the T waves was similarly studied under various conditions, e. g physical work and influence of certain drugs, such as amyle nitrite and skopyl The T waves decreased linearly in amplitude with the rise in pulse frequency. At a certain pulse rate the T waves became isoelectric and at higher values inverted. Th [illegible] pulse showed a rather big variation in different individuals, for instance varying between 115 and 200 beats per minute in lead II

Several clinical reports have been published about the limits of the S—T changes in healthy individuals. It is, however important to notice that the S—T depressions can be measured in different ways. There is a great danger in using a line between two T—P segments as the isoelectric line because these segments are often elevated by positive afterpotentials" In this as in other similar studies [Sjöstrand 1950 (8 9) and Bengtsson 1956 (1)] the isoelectric line is drawn between the P—Q segments of two or more beats.

In an investigation of 125 healthy children and adults of both sexes Bengtsson (1956) (1) found no S—T depression below the P—Q level exceeding 1—1 1/2 mm at any time or in any lead during exercise test. He also emphasized the importance of the appearance and extension of the S—T segment. The normal frequency-dependent S—T depressions often show a slight curved shape while the abnormal S—T depression has an extended plateau shape or is combined with an abnormal T wave In

PREFACE

I wish to express my sincere gratitude to all those who have helped me in connection of this investigation.

Professor Torgny Sjöstrand has assisted me in all respects with his never failing generosity, interest and patience.

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I also wish to thank Mr W. H. Hilton-Brown for pleasant collaboration in the revision of the English in Chapters I and III—VIII, and Mr Nigel Morgan for Chapter II.

M s Britta Eklöf has helped me most effectively w th the typing of the manuscript and Mrs Monica Setterwall has shown great skill in preparing the diagrams.

The investigation has been made possible by a grant from "Folksams rehabiliteringsfond" for which I wish to express my gratitude.

Stockholm May 1961

LARS SANDBERG

CH, CR/CH and CR/CH have been taken.

The method for the investigation is the same as is described in Chapter I

Evaluation of the electrocardiograms

S—T depressions

The S—T depressions are measured in relation to an isoelectric line drawn between two or more P—Q intervals. They are divided into groups according to the following scheme

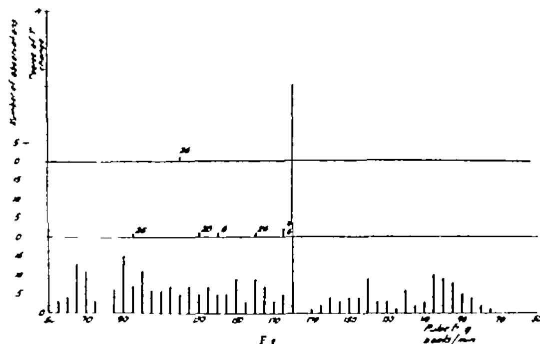
Degree 0 The S—T interval follows the isoelectrical line
" 1 Depression of 0 to 2 mm.
" 2 Depression of 2 to 4 mm.
" 3 Depression of 4 to 6 mm.
" 4 Depression of 6 mm or more

T-depressions

Degree 0 Obvious positive T wave with amplitude corresponding to the other waves.
" 1 Flattened T wave.
" 2 Isoelectric T wave.
" 3 Diphasic T wave.
" 4 Negative T wave.

Results

The S—T and T changes in relation to the pulse frequency during exercise is presented in the following eight diagrams.



Fig

T changes in lead CR CH in relation pulse frequency during and after work. The numerals of the diagram present single diverging cases.

CONTENTS

F g 4

5—T hanges in lead CR /CH in relation t pulse frequency d ri g and fter wo k The numerals in the diagram pr sent n gl di ergi g case

F g 5

T hang l I C R CH lat p lse f quen y during and fter work The numer ls l d m pr se ingl diverging ases.

GENERAL INTRODUCTION

In order to be able to judge the reactions of different persons when doing physical work, for quite a long time now various kinds of exercise tests have been employed. These vary widely in character they comprise knee bendings, raising oneself from a lying to a sitting position, running up a flight of stairs, walking on a treadmill, and pedalling a bicycle ergometer

The use of the bicycle ergometer has many advantages. It allows an objective determination of the size of the load and enables studies of different circulatory parameters during the work, including Ecg tracing.

A test of this kind has been used at Karolinska sjukhuset since 1942 [Sjöstrand 1947 (1), Wahlund 1948 (2)] From 1942 to 1959 about 18000 tests have been carried out. With one exception no serious complications have occurred. In this case, contrary to the regulations, the patient had a cold shower immediately after the work, and got a heart standstill.

The aim of this study has been to obtain norms for the evaluation of various Ecg changes that may occur in connection with exercise tests. As several other authors have pointed out, this can be achieved only by conducting an empirical investigation of a large material.

Selection of the material

A close study was made of those of all the exercise tests performed in the Department of Clinical Physiology of Karolinska sjukhuset during a period of five years, 1951—1955 consisting of 5703 cases, which were considered pathological or positive" In order to study the additional value of making an Ecg examination during a graded exercise test, only cases were included which had normal or practically normal Ecgs at rest, but where Ecg changes developed during or after work.

There are different kinds of Ecg changes developing during exercise tests. This study has been limited to the following groups

1. Changes in the S T T interval
2. Ventricular arrhythmias.
3. Bundle branch blocks.
4. Preexcitation.
5. Atrioventricular conduction disturbances.
6. Atrial fibrillation or flutter

As regards the study of preexcitation only brief reports have been published on the reactions during and after exercise tests. Therefore the investigation was extended to cover all cases of preexcitation.

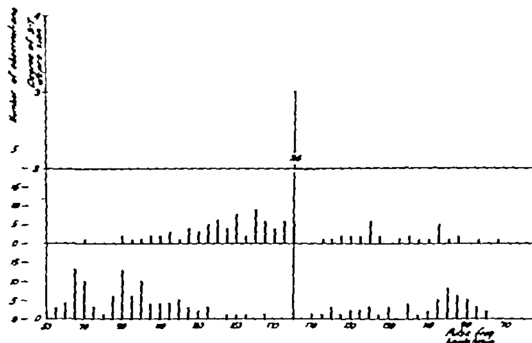


Fig 8

S—T hange in lead CR CH in relation t p lse f q ency during and fter work The numerals in the diagram epresent single dr gong ses.

The S—T and T changes during the orthostatic test are shown in tables 1 and

Degree / Lead	0	1	2	3	4
CR	42				
CR	40	1			
CR	3[illegible]	4		1	
CR	30	11		1	

T ble 1

3 [illegible] orthostatic test.

exceed 170 beats per minute. For women the work loads are 200, 400 600 etc. kpm/min. Work under each load is performed for six minutes. Pulse rates are registered every second minute respiration frequency between the fourth and fifth minutes, and the Ecg is recorded during the fifth minute.

When the patient reaches the upper limit of any of the functions which can restrict his working capacity the test is discontinued, the patient is placed on a bench and an Ecg is recorded as soon as possible. After four minutes rest, Ecg and pulse rates are again registered it desirable they are repeated after some time.

There is very considerable advantage in using a direct writing Ecg apparatus. because this enables the investigator to see immediately on the Ecg strip any suspicious changes and then to stop the test which of course diminishes the risks for the patient.

Electrocardiography

The Ecgs have been recorded by different apparatus, all manufactured by Elema, Stockholm. The "Triplex" is a four channel apparatus, and the "Elema Clinic" a six channel electrocardiograph, both with simultaneous recording of four and six leads respectively From 1955 a direct writing, four channel "Mingograph 42 has been used. By duplicate recordings still more leads have been used.

The leads used were at rest and after work I II III CR IVR, IVR CR CR and sometimes CR After 1955 when the "Mingograph 42 was introduced the corresponding leads were I II III CR CR CR CR and CR When sitting on the bicycl ergometer and during work, only the chest leads were recorded, and the reference electrode was moved from the right arm to the forehead. The leads then obtained were called CH leads (Chest Head) According to Bengtsson (1956) (6) Holmgren et al (1959) (7) and Holmgren and Strandell (1960) (8) the CR and CH leads are, on the whole comparable when used in this connection.

The terms of the leads are those ecommended by the New York Heart Association.

Determination of total amount of hemoglobin

The total amount of hemoglobin was determined by the alveolar carbon monoxide method, which was first described by Sjöstrand (1948)(9 10) and later by Sjöstrand (1953) (11), Carlsten et al. (1954) (12) and Wiklander (1956) (13)

Both before and after the administration of a small amount of carbon monoxide, the carboxyhemoglobin con-

	Degree of T changes					Sum of 1—4 in degrees (S)	Number of observations (*n*)	$\frac{S}{n}$
	0	1	2	3	4			
At rest	41					0	41	0
Standing	40	1				1	41	0.02
300	41					0	41	0
600	40	1				1	41	0.02
900	39	2				2	41	0.05
1200 kpm/min.	38	3				3	41	0.07
Imm. aft. work	41					0	41	0
4 after work	41					0	41	0

Table 5 T changes in lead CR_4/CH

	Degree of S—T changes					Sum of 1—4 in degrees (S)	Number of observations (n)	$\frac{S}{n}$
	0	1	2	3	4			
At rest	40	1				1	41	0.02
Standing	39	2				2	41	0.05
300	36	5				5	41	0.12
600	28	12	1			14	41	0.34
900	18	18	1			20	37	0.54
1200 kpm/min.	10	9	1			11	20	0.55
Imm. aft. work	26	15				15	41	0.37
4 after work	37	4				4	41	0.1

T bl 6. S—T changes in lead CR_4/CH

	Degree of T changes					Sum of 1—4 in degrees (S)	Number of observations (n)	$\frac{S}{n}$
	0	1	2	3	4			
At rest	42					0	42	0
Standing	37	4		1		7	42	0.17
300	38	3				3	41	0.07
600	36	6				6	42	0.14
900	33			1		10	41	0.24
1200 kpm/min.	[illegible]	3				3	22	0.14
Imm. aft. work	41	1				1	42	0.02
4 after work	38	3		1		6	42	0.14

T bl. T hanges in lead CR_4/CH

the pulse frequency above 80 beats. At a frequency of 125 beats per minute the decrease was approximately 15 per cent. This is of importance when the values for heart volume obtained by applying the present technique are compared with those obtained in a sitting or a standing position.

References

Sjo t and T Acta Med. Scand. Suppl 196 687 917

2. Wahlund H Acta Med. Scand Suppl. 5 948

3 D hlst om H S enska Läkartid ingen 46 944 949.

4 Holmgren A and Matt son A H Scand J Clin. nd Lab. I est. 6 57 954

5 Holmgren A. Scand. J Cl and Lab I est. Suppl. 24 956

6 Bengt son E Acta Med Scand 54 5 956

7 Holmgren A Jon son B Levander M Linderholm, H Sjost and T and Strom G Acta Med. Scand. 451259 959.

8 Holmgren A and St andell, T Acta Med Scand. 960. I press

9 Sjo t and T A ta Physiol. Sc nd 6 20 948

Sjost and T Acta Physiol Scand 6 948

Sjostrand T Physiol Re 33 953.

Carlsten A Holmgren A Linroth K Sjost and T and Strom G Act Phy siol. Scand 3 26 954

3 Wiklander O Acta Chir Scand. Suppl. 8 956.

4 Sjost and T P rson l ommunication

5 Kobbe H C ul ory dimension and culatory function during and after pregnancy Thesis, Stockholm 959

6 Sjostrand T Acta Physiol Scand 8 5 4 949

7 Kjellberg, S R., Rudhe L and Sjost and T Acta Physiol Scand. 9 46 919

8 A and P O E perimen l st dies on phy cal orking capacity in relation to sex and ag M ksgaard Copenhagen 952.

9 F etheim B Carcinoma cervical behandlet med abdominothoracal total g strectomi Med undersøkelse en del blodforand ringe hos pa enter med arcinoma Akademisk ryk ngscentral, Osl 953

Hallbe g, L Scand J Cli and Lab I est Suppl 6 955

Norlander O A ta Chi Scand Suppl 99 955

Li roth K Act Med Scand Suppl 3 4 Vol 57 917

3 La son H and Kjellberg S R Acta Ra diolo 9 59 948

24 Kjellberg, S R Rudhe L and Sjost and T Acta Radiol. 3 5 949.

5 Kjellberg, S R Linroth, H Rudhe U and Sjost and T Acta Med. Sca d. 4 446 95

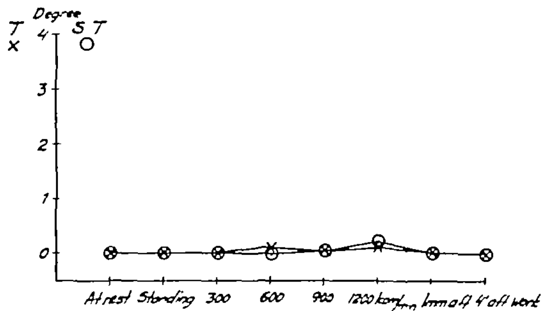
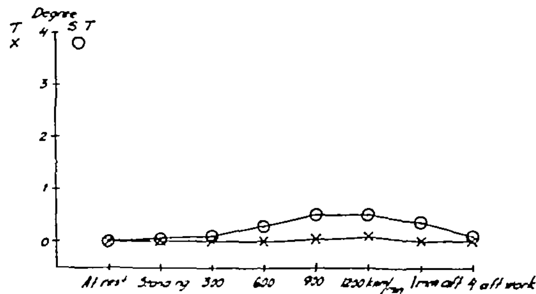


Fig. 9.
A er ge urve in lead CR_4/CH_4.



F g

1 r rt l ad CR CH

an upright position Ecg changes were found in the left and apical leads but *not in the right chest lead* the changes were less common in children than in adults. In Bengtsson s investigation the orthostatic tests were carried out, however in a different way from that employed *here since the upright position* was maintained for only two minutes as compared with eight minutes in our tests.

Different opinions about the limits of the S—T depressions in healthy people have been published. Thus Twiss and Sokolow (1942) (10) consider the limit to be 1 mm. in lead I 1 5 mm. in leads II and III and 2 mm. in lead IV According to Levan (1945) (6) the upper limit of normal is 0.75 mm. in any lead and Björck (1946) (2) considered as normal *only those records in which the sum* of the S—T deviations in the three standard leads is less than 2 mm. Master et al. (1942) (7) accept as the upper limit of normal as little as 0.5 mm. in any lead.

In a recent report by Lepeschkin (1960) (5) where the leads V V V and V were studied, he found none of the apparently normal persons of his material with a true S—T depression of 2 mm. or more, lasting 4 or more minutes.

However the present study is not aimed to show exact normal limits in fractional parts of millimeters for the S—T and T depressions during exercise but to try to demonstrate a typical pattern for the changes during the exercise and orthostatic test for comparison with the patterns in the three groups of cases in chapter III. This and the fact that there are often considerable difficulties in measuring the S—T depressions during exercise at high pulse fre*quencies have convinced the author that* it is a more practically useful method to divide the S—T depressions into classes of two millimeters width instead of measuring the depressions in fractional parts of millimeters.

Material and methods

The material has primarily been taken from the Health Survey of the City of Stockholm 1954 (4)

*In a study of the serum lipids in nor*mal men Carlson (1960) (3) has made a survey of this randomly selected material and collected a number of males without clinical, laboratory or anamnestic signs of heart diseases or other symptoms of interest. Methods and principles for the selection of the material are described *in that report. Of that* material the Ecgs of all male cases between 35 and 50 years, comprising forty two individuals, have been more closely *studied in order to obtain the normal* pattern of S—T and T changes in the left precordial leads during a combined orthostatic and exercise test.

The leads studied in this material are CR/CH leads as is described in Chapter I In forty one cases the leads CR_4/CH CR_5/CH CR_6/CH_1 and CR /CH are *recorded while in one case only* CR_4/

The distribution of the different degrees of S—T and T changes in per cent and their relation to pulse frequency and work load in the four leads is shown in table 11

	T-changes				S—T changes		
	Degree	Per cent.	Pulse freq (beats/min.)	Load (kpm/min)	Per cent.	Pulse freq. (beats/min)	Load (kpm/min)
CH_5	0 1	98			100		
	2	2	120	600			
	3 4						
CH	0 1	100			95		
	2				5	175—180	900—1200
	3 4						
CH	0 1	98			95		
	2				5	145—180	900—1200
	3	2	170	1200			
	4						
CH	0 1	93			98		
	2	5	130—165	900—1200	2	180	1200
	3	2	100	4 aft. work			
	4						

Table 11 Distribution of the different degrees of S—T and T changes in per cent and their relation to pulse frequency and work load in the four leads.

As for other Ecg changes of interest, case 22 a forty year-old man, showed ventricular premature beats during exercise on the highest loads 900 and 1200 kpm/min. No other changes of interest were observed.

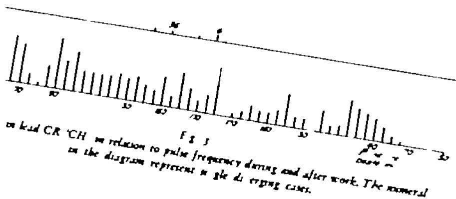
From Fig … and table 11 it appears that in lead CR CH all except one case show no change or only a flatte ning of the T waves wh le only one case has en isoelectric T wave Th s appear already at a pulse rate of 120 beats per minute and at a load of 600 kpm/min.

In lead CR_4/CH no case shows more than a flattening of the T waves and in CR_4/CH only one case has an isoelectric T wave. This change occurs at a high load, 1200 kpm/min., and at a high pulse frequency 170 beats per min.

The situation is similar in CR/CH where two cases show isoelectric T

F g

S T Range in lead CR CH in relation pulse frequenc during and ork Th
n meral in be diagr m pr sent single di ging case



F g 3

in lead CR CH in relation to pulse frequency during and after work. The numeral
in the diagram represent si gle di erging cases.

greater possibilities of including single early cases of ischemic heart disease without manifest symptoms in the age group investigated by us.

Conclusion

Forty two randomly selected healthy men between 35 and 50 years of age were studied with four CR/CH leads during a combined orthostatic and exercise test on a bicycle ergometer In leads CR_4/CH_4, CR_4/CH and CR_5/CH_5 changes consisting in more than a flattening of the T waves were seen only in three cases and they all appeared at loads of 900 kpm/min or more. No case was seen with an S—T depression of 2 mm or more at loads below 900 kpm/min and at pulse rates below 145 beats per minute in leads CR_6/CH CR_4/CH CR_4/CH and CR /CH During the orthostatic test only one case revealed an isoelectric T wave already at a low pulse frequency while no case showed an S—T depression of 2 mm or more

References

Bengtsson E Acta Med. Scand. 54 225 956.

Biorck G Am. Heart J 32.689 946

3 *Carlson L A* Acta Med. Scand 167 1 960

4 *Frisk A R., Holmgren A Strom, G Werko I Westman C and Uttorsson* K E N d Med. 58 437 957

5 *Lepeschkin E* Circulation, Vol. XXII 956 96

6. *Levine J* War Med. 7:3531 945

7 *Master A. M Friedman R. and Dack S* Am. Heart J 41:771 942.

8. *Sjostrand T* Acta Med. Scand. 138 911 1950.

9 *Sjostrand T* Acta Med. Scand. 138:201 950.

10. *Tw s A. and Sobolow M* Am. Heart J 23:498 942.

Fig. 6

5—T hange in lead CR_5/CH in relation pulse frequency during and f er ork. The numeral in he diagr m represent single diverging cases.

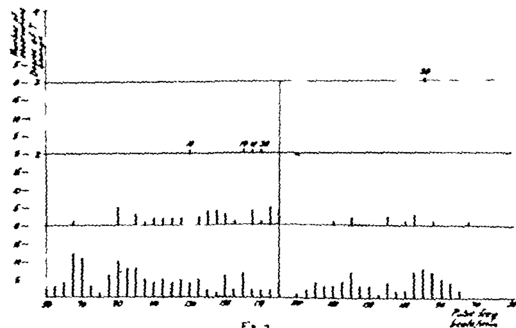


Fig. 7

T hanges in lead CR_5/CH in relation pulse frequency during and after work. The numerals in the diagram represent single diverging cases.

(1948) (20). The usual types of exercise employed here were running upstairs or knee-bending; consequently it was usually not possible to trace the Ecg during the work or to determinate the amount of work performed.

In 1956 Klepzig, Müller and Reindell (21) published an investigation with Ecg recording during work done on a bicycle ergometer and where the standard leads were registered. In their opinion the method was too complicated in comparison with Ecg recording only after exercise.

In 1929 Master and Oppenheimer (33) published their first investigations on the two-step test; later several reports were issued by Master and coworkers (28, 29, 30, 31, 32, 34). According to American literature, Master's two-step test is the exercise test which is now most often employed. This test has been modified in different ways.

Leeds and Kropf (1953) (22) in conformity with several other authors, established the fact that a negative finding in a double two-step exercise test does not exclude the possibility of a latent coronary artery disease. In fact, their attitude was so negative, that they stated "the normal 12 lead Ecg made at rest appears to be of more value than the Ecg made after exercise in the detection of latent coronary artery disease in apparently normal persons."

Simonson and Keys (1956) (49) discussed Master's normal controls and concluded that deviations in S—T depression up to 1 mm represented random variation in a normal population and could not be considered abnormal. Th[illegible] deal mainly with the value of Master's two-step test compared with that of a treadmill in the diagnosis of coronary diseases. They consider that a treadmill is the most suitable instrument for this purpose; they admit, however, that treadmills are available in only a very few hospitals and laboratories and that a simple standardized test, such as Master's two-step test, which can be used without considerations of cost or space, is needed as a substitute, although the steady state is not reached owing to the short duration of the test.

Cosby and Mayo (1959) (6) published their experience of Master's two-step test in coronary disease and emphasized its value. They found that the T wave inversion is a relatively uncommon finding, and when it does occur it is hardly ever accompanied by S—T depression. Thus, S—T depression and T wave inversion appeared to be almost mutually exclusive.

Durham (1953) (7) reported a case where the exercise test was normal a few days or weeks before myocardial infarctions were detected. Similar observations have been made by Simonson and Keys (49).

Lepeschkin and Surawicz (1958) (24) found that, out of 243 persons who were presumably free from cardiac or coronary artery diseases, 26 per cent had abnormal Ecgs according to Master's criteria for the double two-step test.

In a modified Master's two-step test, with Ecg recording also during work, Yu and Soffer (1952) (60) emphasized, among other facts, the value of the Q—T/T—Q quotient as a sign of the myocardial function during work. It is,

Degree / Lead	0	1	2	3	4
CR	42				
CR	39	2			
CR	40	2			
CR	39	3			

Table 2.
S—T changes during orthostatic test.

As a demonstration of the pattern for the S—T and T depressions during the different stages of the test in a normal material like this average curves for the four leads have been drawn accordin^ to the values shown in tables 3—10

	Degree of T changes					Sum of 1—4 in degrees.	Number of observations	$\frac{S}{n}$
	0	1	2	3	4	(S)	( )	
At rest	42					0	42	0
Standing	42					0	42	0
300	41	1				1	42	0.02
600	39	2	1			4	42	0.1
900	39	2				2	41	0.05
1200 kpm/min.	20	2				2	22	0 09
Imm. aft.	42					0	42	0
4 aft. work.	42					0	42	0

Table 3. T changes in lead CR_4/CH_4

	Degree of S—T changes					Sum of 1—4 in degrees	Number of observations	$\frac{S}{n}$
	0	1	2	3	4	(S)	( )	
At rest	42					0	42	0
Standing	42					0	42	0
300	42					0	42	0
600	42					0	42	0
900	39	3				3	42	0.07
1200 kpm/min.	18	4				4	22	0 18
Imm. aft. work.	42					0	42	0
4 after work.	42					0	42	0

Table 4 S—T changes in lead CR_4/CH_4

Lindgren (1952) (25) and Bengtsson (1957) (16) have described the typical, positive results of exercise tests obtained for patients after their recovery from an infectious disease complicated by myocarditis.

Orthostatic Ecg test

According to Åkesson (1936) (61), S—T T depressions in arterial orthostatic anemia depend upon an insufficient coronary blood supply in relation to the oxygen requirements. He also states that "as a typical for the healthy heart and the heart without impairment of blood supply the T waves became higher on exercise and lower following nitroglycerine"

Other authors, such as Evert (1938) (9) Nordenfeldt (1941) (37), Schenetten (1943) (46) and Bengtsson (1948) (2) attribute the cause of the Ecg changes to alterations in the vegetative tonus.

In order to elucidate this problem Sjöstrand (1950) (50 51) studied experimental variations in the T waves. He concluded that there are at least two factors which influence the height of the T waves. One generally correlated to the pulse rate and the other related to the position of the body He therefore emphasizes that, when interpreting electrocardiograms in cases of suspected myocardial disease account must be taken of the physiological variations caused by changes of the heart rate and of the blood d tr bution

Sjostrand n t ation also showed that in no health h t the T waves diminished line n pl tud with the rise in pulse r generally followed the sam r s under the influen al work and moderate amylnitrite effect and sometimes following changes of position.

Åkesson s view on an increase in the height of the T waves following exercise, has been previously referred to it is based on observations of Ecg recordings after and not during exercise. After exercise, the T waves rose also in Sjöstrand s material. This might explain the difference in opinion

It seems important to point out that even if in some cases, S—T T changes are dependent upon insufficient coronary blood supply to the myocardium one is not justified in stating that all S—T T depressions are due to one and the same cause There may be several factors which produce the same Ecg patterns as was shown by Sjöstrand (1950) (50, 51) among other investigators.

Orthostatic S—T T depressions are described in the investigations of Vasoregulatory asthenia carried out by Holmgren et al. (13—17). These depressions, as well as S—T T depressions occurring during exercise tests of a special type are regarded as signs of vegetative imbalance in patients without organic heart diseases. This has been described elsewhere.

For these reasons it seems very important to combine an exercise test with

	Degree of S—T changes					Sum of 1—4 in degrees (S)	Number of observations (n)	$\frac{S}{n}$
	0	1	2	3	4			
At rest	41	1				1	42	0.02
Standing	40	2				2	42	0.05
300	34	6				6	40	0.15
600	20	22				22	42	0.52
900	9	29	1			31	39	0.8
1200 kpm/min.	4	15	2			19	21	0.91
Imm. aft. work	21	21				21	42	0.5
4' after work	32	9	1			11	42	0.26

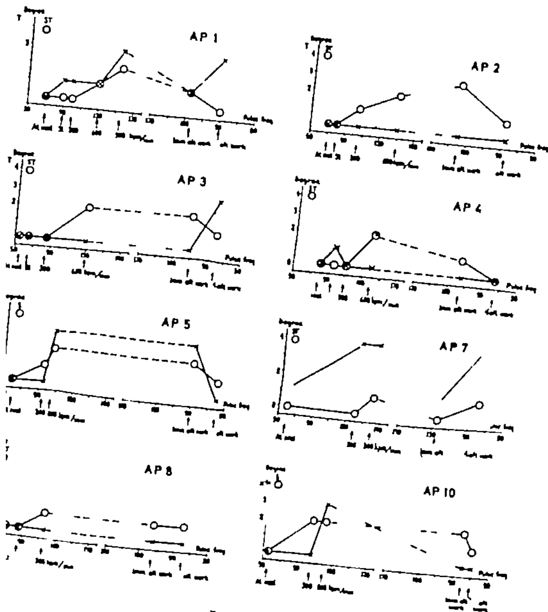
Table 8. S—T changes in lead CR_4/CH

	Degree of T changes					Sum of 1—4 in degrees ( )	Number of observation ( )	S
	0	1	2	3	4			
At rest	41	1				1	42	0.02
Standing	31	10		1		13	42	0.31
300	32	9				9	41	0.22
600	24	18				18	42	0.43
900	25	14				18	41	0.44
1200 kpm/min.	11	9	2			13	22	0.59
Imm. aft. work	38	4				4	42	0.1
4' after work	33	8		1		11	42	0.26

Table 9. T changes in lead CR_4/CH_5

	Degree of S—T changes					Sum of 1—4 in degrees (S)	Number of observations (n)	$\frac{S}{n}$
	0	1	2	3	4			
At rest	41	1				1	42	0.02
Standing	39	3				3	42	0.07
300	32	8				8	40	0.2
600	21	21				21	42	0.5
900	6	34				34	40	0.85
1200 kpm/min.	3	16	1			18	20	0.9
Imm. aft. work	1	21				21	42	0.5
4 after work	32	10				10	42	0.24

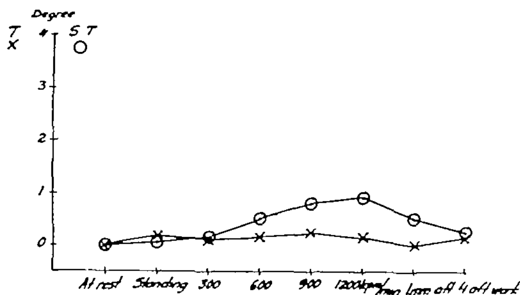
Table 10. S—T changes in lead CR_4/CH



Ecg lead

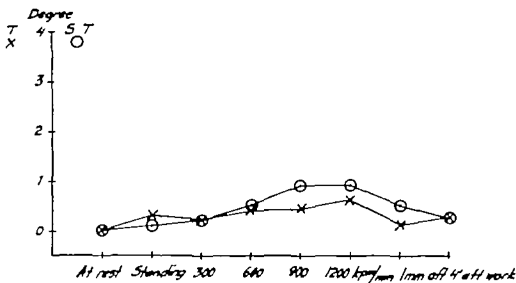
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AP CR CII	AP 4 CR/CII
AP IV R IV H	AP 7 CR CII
AP x CR CII	AP o IV R IV H

Fig 3



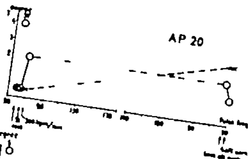
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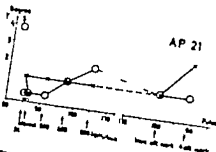
A er ge curv in lead CR_5/CH_5.

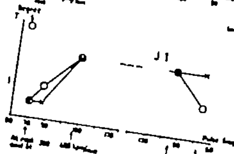


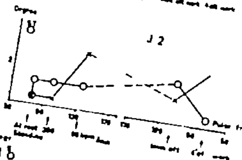
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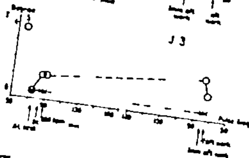
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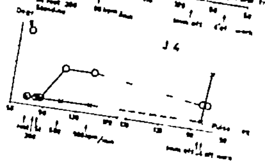


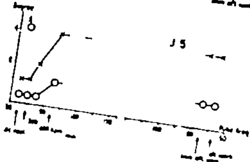


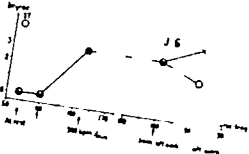












Ecg lead

AP CR CII
J CR CII
J IV R IV II
J CR CII

AP CR CII
J CR/CII
J 4 CR CII
J 6 CR CII

waves at rather high loads, 900 and 1200 kpm/min. In a third case an inverted T wave is seen four minutes after work at a pulse frequency of 100 beats per min.

T changes consisting of more than a flattening have thus been seen only at loads of 900 kpm/min. or more in leads CR/CH, CR/CH and CR/CH.

When studying the S—T changes it is revealed that none of the cases shows an S—T depression of 2 mm or more in lead CR/CH. This limit is exceeded in CR/CH in only two cases, in lead CR/CH in two cases and in lead CR/CH in one case but first at loads of 900—1200 kpm/min.

Thus there was no case with an S—T depression of 2 mm or more at loads below 900 kpm/min. in any leads used.

When studying the four average curves Fig. 9—12 some interesting features may be noticed.

In lead CR/CH the S—T and T segments were on the average unchanged in standing position during and after work. In leads CR/CH, CR/CH and CR/CH the average changes were more frequent particularly the S—T changes. The average values during work never reached degree 1 and the average values of the orthostatic S—T and T depressions were low.

There was also a tendency to further T depressions during the first four minutes after work in leads CR/CH and CR/CH, *while throughout there was a tendency to elevation of the S—T levels in leads CR/CH, CR/CH and CR/CH during the same time as is shown in Fig. 10—12.*

It seems evident that most pronounced changes are found in leads CR/CH, CR/CH and CR/CH in a normal material which is important to consider when interpreting exercise Ecgs of suspected pathological cases.

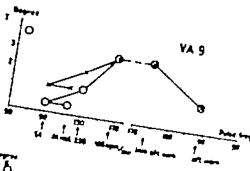
During the orthostatic test, Tables 1—2, no case but one shows a more pronounced change than a flattening. In this case there is an isoelectric T wave in both CR and CR at a pulse frequency of 85 beats per minute.

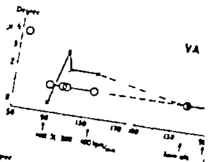
No case shows an S—T depression of 2 mm or more during the orthostatic test.

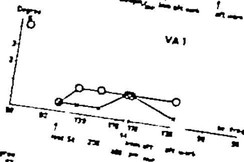
Discussion

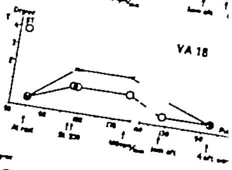
As is pointed out elsewhere several reports of normal values for S—T and T changes in connection with exercise tests have been published. Most of them do not include Ecg recording during but only after work. For this reason, among others, the only investigation comparable with the author's is that published by Bengtsson 1956 (1).

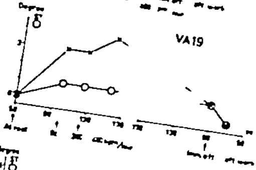
In contradiction to our results Bengtsson found no S—T depression exceeding 1—1½ mm during exercise among healthy children and adults of both sexes in any lead or at any time. The explanation may be that our material comprises men between 35 and 50 years whereas Bengtsson has an upper limit of 40 years. Statistically there ar

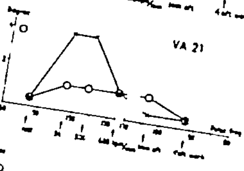


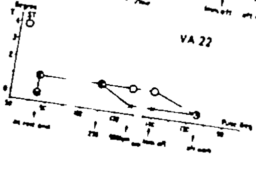


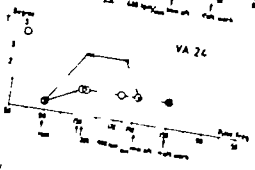












V A CR CH F g lead
CR CH
R CH
H

V A CR CH
V A CR CH
V A CR CH
V A CR CH

F g

CHAPTER III

STUDIES ON THE S T AND T INTERVALS DURING EXERCISE TESTS

Introduction

One of the most usual purposes, for which electrocardiographic exercise tests are employed, is to investigate the cause of more or less pronounced pains in the chest region. This symptom may appear not only in typical organic changes in the coronary arteries but also under other conditions, e. g. myocardial injuries of an infectious etiology and as one of the symptoms connected with functional disturbances of different kinds.

Since angina pectoris is considered to be a sign of a deficient oxygen supply to the myocardium, which is particularly apparent after physical and psychical strain, an Ecg at rest often fails to give any decisive, objective proofs.

In order to study the heart under these conditions of strain different methods for loading the circulation have been tried, such as physical work or anoxemia.

The majority of investigators when studying the S—T and T changes in exercise tests, have used the degree of depression of the S—T interval from the isoelectric line as an index of the pathologic event. It must be emphasized, however that the shape of the S- T and T intervals also changes significantly. The aim of this investigation has been to discover the pattern according to which the S—T and T changes are manifested at different stages during the exercise tests.

Review of the literature

The first author to publish Ecg changes in the S—T and T interval in connection *with physical work, seems to be* the pioneer in Electrocardiography Einthoven (1908) (8) He described the "increase in the height of the P and T waves and a depression of the P—R segment and a negative T in lead III which became positive."

Goldhammer and Scherf (1933) (11) described a case where anginal pain S- T depression and ventricular premature beats of different origin developed *after running up a flight of stairs. The* following year the same authors recommended the exercise test for the early diagnosis of angina pectoris.

In the German literature, studies on exercise tests have been published, for example by Reindell (1938) (42), Reindell and Delius (1941) (43) Holtzmann and Wuhrmann (1936) (19) and Kienle

1 Case	2 Abnormal ... ( ) ... and ...	3 Changes of the T waves during increasing pulse rate following work.	4 Changes of the S—T intervals during increasing pulse rate following work.	5 Changes of the T waves during orthostatic test	6 Changes of the S—T intervals during orthostatic test	7 Changes of the T waves after work.	8 Changes of the S—T intervals after work
AI 1	( )	+	+	(+)	0	+	(—)
AI		0	+	0	0	0	—
AI 3		0		0	0	+	(—)
AI 4		0	+	(+)	0	0	(—)
AI 5		+	+			—	(—)
AI		+	(+)			+	(+)
AI 8	+	0	(+)	0	0	0	U
AI 10	—	+	+			0	(—)
AP 11	+	(+)	(+)	0	0	0	(—)
AI 13	—	0	+	0	0	0	U
AI 14	—	0	+	0	0	0	(—)
AP 15	(—)	0	(+)	0	0	0	(—)
AP 16	—	0	+	0	0	0	U
AI 17	(+)	+	+	(+)	(+)	U	(—)
AI 18		+	+	0	0	+	(—)
AP 19		+	+			+	(—)
AP 20	—	0	+	0	0	U	(—)
AP 1	(+)	(+)	+	(+)	0	+	U

Table 1. The behaviour of the S—T and T during different stages of the test. Group AP

furthermore, interesting to note that false negative test results may be obtained in about 20 per cent of the cases of angina pectoris, if tracings are not made also during exercise. Moreover these authors point out that Ecg abnormalities, indicating coronary insufficiency may be observed, both during and after exercise, in patients not suffering from angina pectoris.

Yu et al. (1951) (59) compared the method in which a treadmill is utilized, with the modified Master's two-step test, previously mentioned. They found distinct advantages in registering a precordial lead Ecg with a direct writing instrument during treadmill walking.

The importance of Ecg tracings, both after and during exercise is stressed by several authors, among whom are Yu and Soffer (1952) (60) Simonson and Keys (1956) (49) Sandberg (1957) (44) and Åstrand (1960) (61).

Biörck (1946) (3) Biörck and Pannier (1947) (5) and Biörck and Dalhamn (1950) (4) studied the value of the hypoxemia test and compared it with that of Nylin's exercise test (38 39 40 41) in the diagnosis of coronary disease. They found that the two tests were of about the same value. It should be pointed out, however that this exercise test does not include Ecg tracing during the exercise.

In the comparison, which Sjöstrand (1951) (52) made, between the bicycle ergometer test and hypoxemia tests, he recommended that, in most cases, the work test should be applied first, and the hypoxemia tests reserved for subjects who cannot perform the bicycle work.

Bengtsson (1956) (1) has published the results of a fundamental investigation of a healthy material consisting of 84 children and 41 adults, which is further discussed in chapter I.

In their studies of Vasoregulatory asthenia, Holmgren et al (1957—1959) (13—17) showed that a relationship existed between this state and the S—T and T depressions of a diffuse type over the left ventricle during orthostatic and exercise tests. After a period of physical training both the changes and the subjective symptoms had practically disappeared. These investigators stated that the Ecg changes reported can be characterized as sympathicotonic because Ecg changes of a similar type can be provoked transiently in experiments where adrenaline is administred intravenously and increased sympathetic tone is induced in human subjects. The disappearance of the Ecg changes after physical training also indicates that they are not due to disturbances of an organic nature.

According to their experience, when patients with myocarditis are examined at rest, the Ecgs sometimes showed during the orthostatic tests and during and after the exercise tests, characteristic T wave changes over a localized area of the precordium.

They also considered that the Ecgs in Vasoregulatory asthenia differ from those of coronary artery disease, for in the latter condition, the orthostatic tests are normal, whereas characteristic S—T and T depressions occur during work, and especially in the first few minutes after work.

Among other investigators, Levander

(roup \ \

1	\ d l d \ l ad l hanges	3 Changes of the T es during in creasing pulse rat following work	4 Changes of the S T intervals during increasing pulse at follow work	5 Changes of the T wa es during orthostatic test	6 Changes of the S—T intervals during ortho-static test	7 Changes of the T waves after work	8 Changes of the S—T intervals af er work
\		+	+	U	U	—	—
\ 1		( )	L	+	U	U	U
\ \ 1	( )		+	0	(+)	(—)	U
\ \ 18			(+)	+	(+)	(—)	0
\ \ 19			(+)	+	(+)	(—)	(—)
\ \ 1		( )	( )	+	(+)	0	(—)
\ \ —		( )	(+)	( )	(+)	0	(—)
\ \ 4			(+)	+	(+)	U	U

C roup M

M 2		( )	t	+	L	U	(—)
M 10	( )		( )	+	L	0	U
M 15			( )		0	+	U
M 16		+	+	+	0	(—)	U

Table 14 The beha ion of the S—T and T during different stages of the test

Ecg recordings made also during an orthostatic test as this should make it possible to differentiate between organic and functional S—T T depressions.

Material

The cases have been divided into four groups

The first group called I comprises cases with normal or almost normal Ecg at rest, where S—T T depressions developed during the exercise test and the patients later got a myocardial infarction. This group consisted of eleven cases.

The second group group AP consisted of twenty one cases with a typical history of effort angina, which showed the same Ecg changes as those used in the former group.

When following up the latter patients, it was found that three of them had aquired myocardial infarctions and two of these had died of this disease. For this reason these cases were transferred from group AP to group I

The third group VA, consists of eight cases included in the material used by Holmgren et al. (13—17) in their investigation of Vasoregulatory asthenia (VA). This material represents sympathicotonic Ecg changes in cases without objective signs of cardial disease. Six of them have been heart catheterized, showing a normal heart function.

The fourth group M consists of only four cases, who had earlier been treated in the hospital for acute myocarditis. A requisite condition was that the patients had had unequivocal Ecg changes in the S—T T interval developing in connection with an infectious disease.

Results

In order to show the results in a manner which can be readily understood diagrams have been made in each case of the S—T and T changes in the exercise tests.

The leads demonstrated are those where the S—T T depressions are most pronounced.

In some cases, particularly in those with a sympathicotonic Ecg reaction, it is difficult to show as much as is desirable but this method seems to be the most expedient for practical use.

The leads used are shown under the diagrams.

From tables 12—14 and 15 the following conclusions may be drawn considering the average patterns for the three groups, with due reservation on account of the small number of cases.

Group AP+I

1 Increasing or unaltered T depression during increased pulse rate following exercise.
2 The S—T depressions do not show any gradual increase during increased pulse rate, but seem rather to be correlated to the level of the strain imposed on the subject
3 Absence of orthostatic S—T T depressions.
4 The T waves vary in different cases without any typical pattern after work.
5 Decreasing or unaltered S—T depressions after work
6 No obvious correlation between the S—T and T depressions during the orthostatic and exercise test.

Group VA

1 Progressive lowering of the T waves during increased pulse rate following exercise.
2 Increasing S—T depression during increased pulse rate following exercise
3 Lowering and often inversion, of the T waves in the orthostatic tests.
4 Slight depression of the S—T segments in the orthostatic tests.
5 No further increase in the degree of T depressions after work.
6 No further increase in the degree of S—T depressions after work.
7 The S—T and T depressions are similar in an upright position and during exercise, largely in accordance with the pulse rate.

Group M

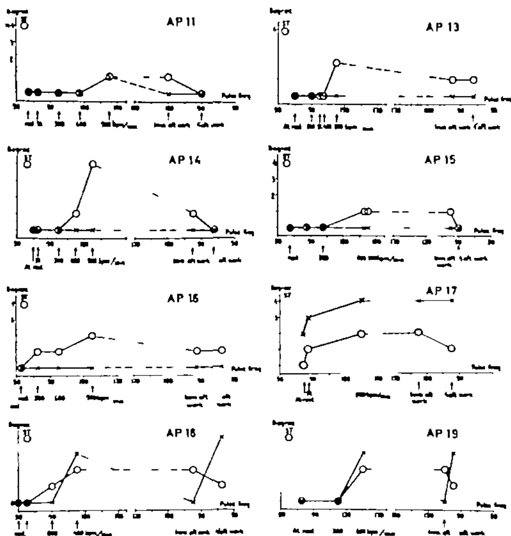
1 Increasing T depression during increased pulse rate following exercise
2 Increasing or unaltered S—T depressions during increased pulse rate following exercise.
3 Depression of the T waves in the orthostatic tests.
4 Absence of or unaltered S T depressions in the orthostatic tests.
5 The T waves vary in different cases without any typical pattern
6 No further increase in the degree of S—T depression after exercise.
7 The changes in the S—T intervals have no parallel in the orthostatic tests and during exercise

The average curve

In ord[illegible] representative of ea[illegible] group [illegible] curves have been [illegible]ted

During each stage of [illegible] degree units of all cases in ea[illegible] are summed up (S) and the values thus obtained are divided by the number of [illegible]ases (n) as is shown in tables 16—19

The average values are used for the [illegible] of the following curves.



Ecg lead

AP	*CR[illegible]/CH*	*AP 3*	*CR[illegible]/CH*
AP 4	*CR[illegible]/CH*	*AP 5*	*CR[illegible]/CH*
AP 6	*CR[illegible]/CH*	*AP 17*	*CR[illegible]/CH*
AP 8	*CR /CH*	*AP 9*	*CR[illegible]/CH*

Fig 4.

GROUP VI

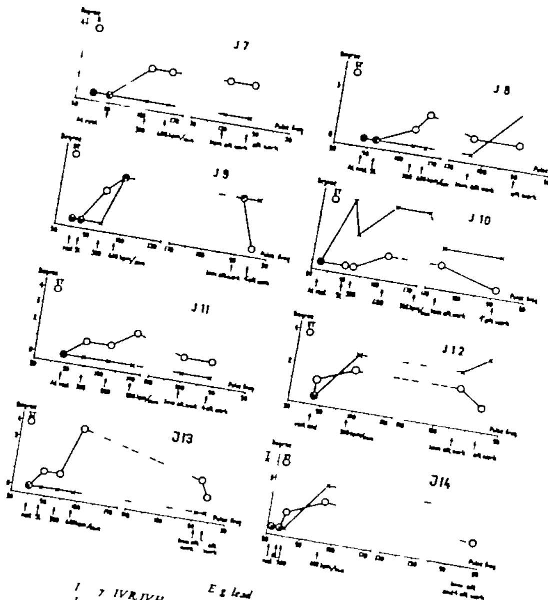
T changes

	Degree of depression					Sum of 1—4 in degrees (S)	Number of observations ( )	S/n
	0	1	2	3	4			
At rest	2	1	1			3	4	0.75
Standing			1		3	14	4	3.5
1st load		2			2	10	4	2.5
2nd „			1		3	14	4	3.5
3rd „			2		1	8	4	2
Imm. aft. work	1	2	1			4	4	1
4 after work	2	1			1	5	4	1.3

S—T changes.

	Degree of depression					Sum of 1—4 in degrees (S)	Number of observations ( )	S/n
	0	1	2	3	4			
At rest	2	2				2	4	0.5
Standing	2	2				2	4	0.5
1st load	2	2				2	4	0.5
2nd		3				3	3	1
3rd „		1	2			5	3	1.7
Imm. aft. work		4				4	4	1
4 after work	1	3				3	4	0.75

Table 19

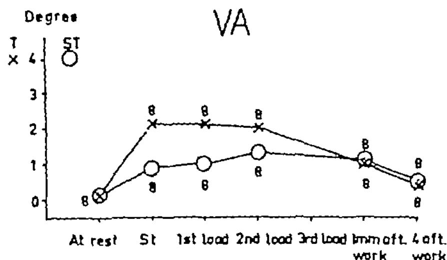


E g lead

I 7 IVR/IVH
I 9 IVR/IVH
I CR CH
I 3 IVR IVH

I 8 IVR/IVH
I CR_1/CH
I CR_2/CH
I 4 CR_3/CH

F g 6



F g Average curve of group VA.

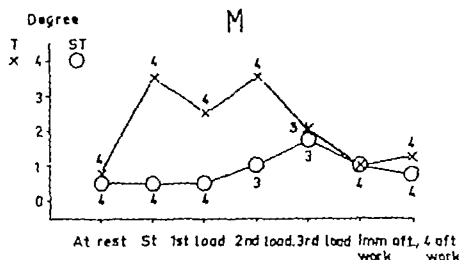


Fig A er ge curv f group M

The differen e betw en the orthosta tic reaction n groups AP and I n the one hand and th t f p VA and M on the other l r l tr st d as well as the association between the S—T and T changes in group VA, in contrast to the dissociation in group M

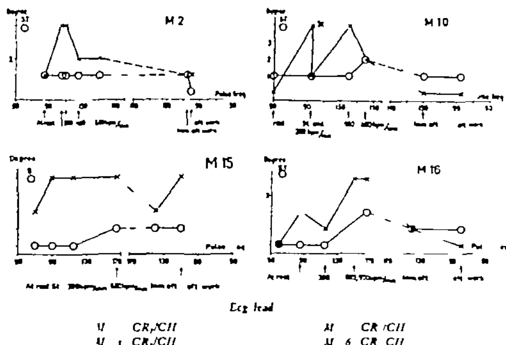


Fig. 8

When comparing the changes in the S—T and T intervals the following criteria are considered

+ = Obvious increase in the degree of S—T or T alteration

(+) = Increase by only one unit in the degree of S—T or T alteration e. g. 1—2.

— = Obvious decrease in the degree of S—T or T alteration.

(—) = Decrease by only one unit in the degree of S—T or T alteration e. g. 2—1

U = The shape of the S—T or T intervals remains unchanged.

o = No change of the S—T or T intervals (normal pattern).

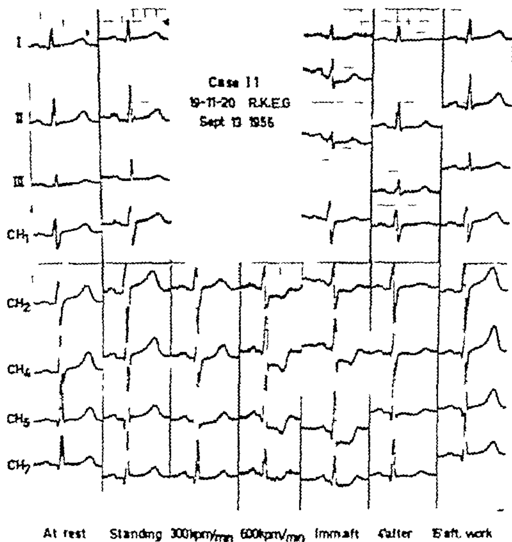

Case 11
19-11-20 R.K.E.G
Sept 13 1956
I
II
III
CH1
CH2
CH4
CH5
CH7
At rest
Standing
300kpm/min
600kpm/min
Imm.aft
4'after
15'aft. work

Fig. 3

1 Case	2 Associated (+) or dissociated S—T and T changes	3 Changes of the T waves during increasing pulse at following work	4 Changes of the S—T intervals during increasing pulse rat following work	5 Changes of he T w es during orthostatic test	6 Changes of the S—T in ervals during orthostatic test	7 Changes of the T wa es after work	8 Changes of the S—T int rvals f er w rk
I 1	+	+	+	0	0	U	—
I 2	(+)	+	(+)	0	(+)	+	—
I 3	—	0	(+)	0	(+)	0	(—)
I 4	—	0	+	0	0	+	U
I 5	(+)	+	(+)	U	0	U	U
I 6	+	+		0	0	(+)	(—)
I 7	—	0	+	0	0	0	U
I 8	—	0	+	0	0	+	U
I 9	+	+		0	0	U	—
I 10	—	+	(+)		0	U	—
I 11	—	0	+			0	U
I 12	+	+	+	0	(+)	(+)	(—)
I 13	—	0	+	0	(+)	0	(—)
I 14	+	+	+	0	0	U	U

Table 13 The beha iour of the S—T and T during diff rent stages of he test Group I

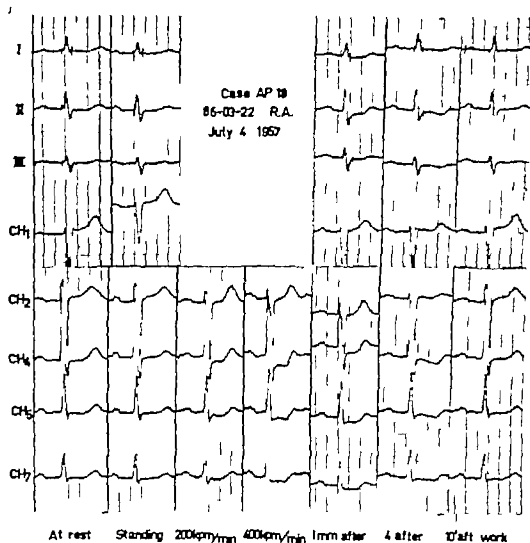

I
II
III
CH1
CH2
CH4
CH5
CH7
Case AP 19
86-03-22 R.A.
July 4 1957
At rest
Standing
200kpm/min
400kpm/min
Imm after
4 after
10'aft work

Fig 5

The AP + I group

Change	3	4	5	6	7	8
+	15	24	1		9	0
(+)	2	8	4	5	2	1
—					1	5
(—)						16
U			1		7	10
0	15		21	22	13	
Sum	32	32	27	27	32	32

The VA group.

Change	3	4	5	6	7	8
+	5	2	5			
(+)	3	5	1	6		
—					1	1
(—)					3	3
U		1	1	2	2	3
0			1		2	1
Sum	8	8	8	8	8	8

The M group.

Change	3	4	5	6	7	8
+	3	1	4		1	
(+)	1	2				
—						
(—)					1	1
U		1		2	1	3
0				2	1	
Sum	4	4	4	4	4	4

Table 15. Summary table of tables 12—14. The numerals 3—8 represent the different stages of the test and are the same as are used in tables 12—14

S—T and T changes during orthostatic test during and after exercise, in groups VA and M

In spite of the small number of cases, some interesting facts were observed

A common feature of both groups is the positive orthostatic Ecg reaction remaining during work. This is as is earlier emphasized by among others *Bengtsson (1956) (1)* mainly characterized by T depressions. These changes are associated with S—T depressions in the VA group but not in the M group. This appears to afford a means of distinguishing between the two groups.

GROUP AP

T changes.

	Degree of depression					Sum of 1—4 in degrees (S)	Number of observations (n)	S/n
	0	1	2	3	4			
At rest	16	1	1			3	18	0 1
Standing	11	2		1		5	14	0 36
1st load	14	2			2	10	18	0 56
2nd	8	2		4	1	18	15	1 2
3rd „	4	2		1		5	7	0 7
1mm. aft. work	12	3			3	13	18	0 7
4 after work	11			4	3	24	18	1 3

S—T changes.

	Degree of depression					Sum of 1—4 in degrees (S)	Number of observations (n)	S/n
	0	1	2	3	4			
At rest	18					0	18	0
Standing	13	1				1	14	0 07
1st load	10	5	3			11	18	0 61
2nd	1	6	8			22	15	1 5
3rd	2		4		1	12	7	1
1mm. aft. work	1	9		1		26	18	1 4
4 after work	5	13				13	18	0 72

Table 16.

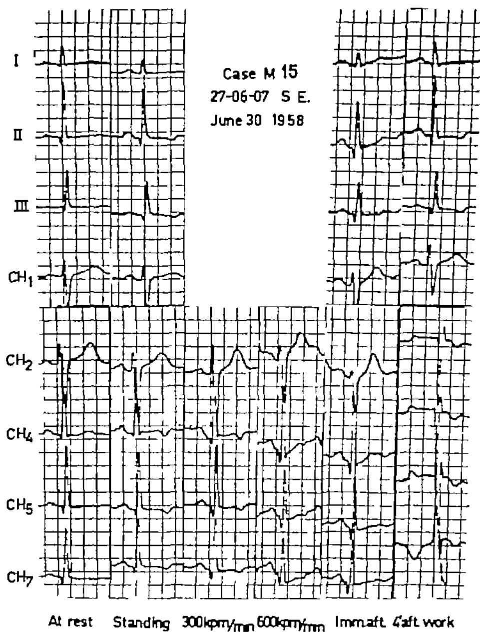
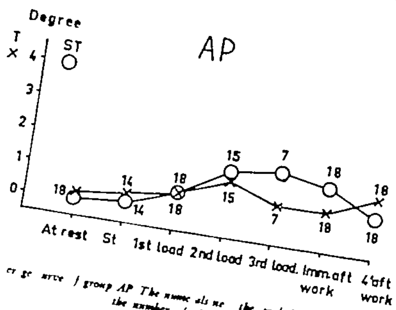
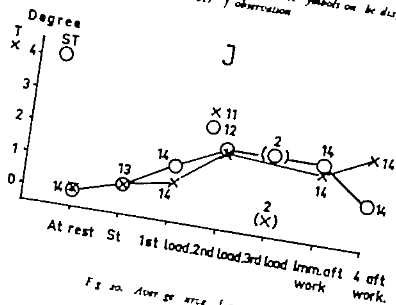

Case M 15
27-06-07 S E.
June 30 1958
I
II
III
CH1
CH2
CH4
CH5
CH7
At rest
Standing
300kpm/min
600kpm/min
Imm.aft.
4'aft. work

Fig. 38

On comparison the two average cur ves AP and I are seen to differ in one respect the I curve shows a more pronounced T depression during and immediately after work than the AP curve. This may be explained by the fact that the changes in group I hav a more serious significance than those of the AP group and thi in agreement with the later myoca d al infarction in the cases of group I



F g 9 A er ge arve f group AP The nume als ne the ymbols on he diagram indicate the number f observation



F g 10. Aver ge arve f group I

S—T and T changes after exercise, in groups VA and M

The results obtained by studying the interval "immediately after work — "four minutes after work" showed no increase in the S—T and T depressions in all but one case. This divergent case, M 15 (Fig 28) showed inversion of the T waves which was of the same type as that found in an upright position

In the results given in tables 12—15 only the lead is shown where the changes are most pronounced. It must be pointed out, that all leads used have to be studied in order to get further information. This applies particularly when distinguishing sympathicotonic from myocardial S—T T depressions. The former are most often spread over the left heart but sometimes also over the right. On the other hand, the Ecg changes in cases of myocarditis are often localized in a limited area of the chest. This material is too small, however to allow of any conclusions beeing drawn in this respect.

Yu and Soffer (1952) (60) and Lepeschkin and Surawicz (1958) (24) have pointed out that Ecg abnormalities, indicating coronary insufficiency according to Master's criteria, are observed during and after exercise in patients presumably free from cardiac or coronary artery disease. These authors do not discuss sympathicotonic Ecg changes at all. It is, however a well known fact that human subjects develop S—T T depressions due to a sympathicotonic cause· this is particulary the case in women and young persons who display anxiety or psychosomatic symptoms.

In the material studied by Lepeschkin and Surawicz, group C contained subjects whose exercise tests were positive, and who were consequently considered to be abnormal. This group must, however include also cases with sympathicotonic Ecg changes. According to our experience, these changes may be expected to occur all the more readily when bearing in mind the results of the orthostatic tests, where, according to their criteria, abnormal Ecgs were found in 48,4 per cent of the subjects, i e. a far higher percentage than in the other groups.

Unfortunately the method applied in the orthostatic test is not described but our experiences show that it is of great importance that an upright position is maintained for a sufficiently long period in the method used in the author's investigation eight minutes are required. Without information on pulse rates at rest, and during the orthostatic tests, it is difficult to say anything about the cause of the high frequency of positive findings in Lepeschkin and Surawicz's group D but this may at least partly be due to the method used in their investigation.

In accordance with the findings of Scherlis et al. (1950) (48) Smith (1950) (53) and Thomas (1951) (55) Lepeschkin and Surawicz (1958) (24) stressed that in normal persons, Ecg abnormalities after exercise last less than two minutes, whereas, according to Littman and Rodman (1951) (26) in persons with coronary insufficiency they last

Discussion

S—T and T changes during orthostatic test during and after exercise in cases of ischemic heart disease

It is evident from tables 12 and 13 that in the cases of ischemic heart disease, groups AP and I S—T depressions appearing during or after exercise are more common than T depressions and there is no constant relation between them in the orthostatic tests and during increasing pulse rates following exercise.

Some cases, AP 1 AP 4 AP 17 AP 21 and I 10 showed a combination of S—T T changes of the type that is present in cases of ischemic heart diseases and such occurring after acute myocarditis and in sympathicotonic individuals.

The best explanation for this would be that orthostatic Ecg reactions are likely to occur with the same frequency in cases of this type as in any randomly mixed material.

The duration of the S—T and T changes after exercise in group AP + I

It has sometimes been emphasized that a typical feature of coronary disease is, that the S—T and T changes show a further increase during the first few minutes after the exercise has been finished. This was relevant, as regards T depressions, for only about one-third of this material (11/32) Thirteen cases showed no T depression at all, seven remained unaltered, and in one case the changes decreased. In respect of the S—T depressions, twenty one cases showed decreased changes and ten remained unaltered.

1 *Goldhammer S & Scherf D* Ztschr f klin. Med. 22 134 1932.

12. *Greuin K E.* Some Supplementary Leads in Clinical Electrocardiography Thesis, Sthlm 1948.

13. *Holmgren, A., Jonsson, B., Levander M Linderholm, H Sjöst and T and Ström, G* Acta Med. Scand. 58:413 1957

14. *Holmgren A., Jonsson, B., Levander M Linderholm, H Mossfeldt, F Sjöstrand T and Ström, G* Acta Med. Scand. 58:437 1957

5 *Holmgren A. and Ström, G* Acta Med. Scand. 164 113 1959.

6. *Holmgren, A., Jonsson, B Levander M Linderholm, H Mossfeldt, F Sjöstrand T and Ström, G* Acta Med. Scand. 165 89 1959.

17 *Holmgren A., Jonsson, B Levander M Linderholm, H Sjöstrand T and Ström G* Acta Med. Scand. 165,239 1959

18. *Holmgren A. & Strandell, T* Acta Med. Scand. 1960. In press.

9. *Holtzmann, M & Wuhrmann, F* Dtsch Med. Wchnschr 6 -64 1936, 62-685 936 62 379 1936.

20. *Kienle F* Das Belastungselektrokardiogramm und das Steh-EKG. Leipzig 1948 Georg Thieme.

Klepzig, H Müller D & Reindell, H Ztschr f Kreislaufforsch. 45 (9—20) 74 956.

22. *Leeds, M F & Kropf S. S* Calif Med. 79 36 953.

3 *Lepeschkin, E* Modern Electrocardiography Vol 951 Williams & Wilkins Co., Balt more U.S.A.

24 *Lepeschkin, E & Surawicz B.* New Engl. J of Med 58 51 1958

5 *Levander Lindgren M* Acta Paediatrica, Suppl 9 95

6. *Littman D and Rodman, M H* Circulation 3 5 5 95

7 *Lozada, B & Tempone V D* Acta Cardiolog 1 6 958

8. *Master A M L S M* Bull 40 346 94

29. *Master A M* J Med 1 84 950

30. *Master A. M Field L. E., Donoso, E.* New York State J of Med. 57: 051 957

3 *Master A. M & Jaffe H L.* J Mt. Sinai Hosp 7 619 1941

32. *Master A. M Nuzzie S., Brown R. C., Parker R. C.* J-or.s Am. J Med. Sc. 207:435 1944.

33. *Master A. M & Oppenheimer E. T* Am. J Med. Sc. 77:223 1929.

34. *Master A. M Pordy L., Chesky K* JAMA 15 -458 1953.

35 *Mattingly T W Fancher P S Bauer F L. and Robb G P* Army Med. Serv Grad. School Research Report. 1—54. Sept. 1954. Washington, D. C., Walter Reed Army Medical Center

36. *Myers, G B & Talmers F N* Ann. I t Med. 43:136 1 955

37 *Nordenfeldt, P* Acta Med. Scand. Suppl. 1 9 941

38 *Nylin G* Acta Med. Scand. Suppl. 78:64 936.

39. *Nylin G* Zentralbl. f inn. Med. 58 529 937

40. *Nylin, G* Acta Med. Scand. Suppl. 93 938.

4 *Nylin G* Cardiologia, 8:163 1944.

42. *Reindell, H* Dtsch Arch. f klin. Med. 182 5:65 938.

43 *Reindell, H & Delius, L.* Klin Wchnschr 20:497:1941

44. *Sandberg, L.:* Nord. Med. 58 17 9 957

45 *Schaefer H and Trautwein W* Pflügers Arch. 51:457 949.

46. *Schemetten, F P N* Arch. f Kreislaufforsch. 326 943.

47 *Scherf D & Schaffer A. J* Am. Heart J 43:927 952.

48. *Scherlis, L., Sandberg, A. A., Wener J Doorbos J & Master A. M* J Mt Sinai Hosp. 27:248 950.

49. *Simonson E. and Keys A.* Am. Heart J 52 831 956.

50. *Sjöstrand T* Acta Med. Scand. 38 9 1950

5 *Sjöstrand T* Acta Med. Scand. 138:2 950.

52. *Sjostrand T* Scand. J of Clin. and Lab. Invest. 3 952.

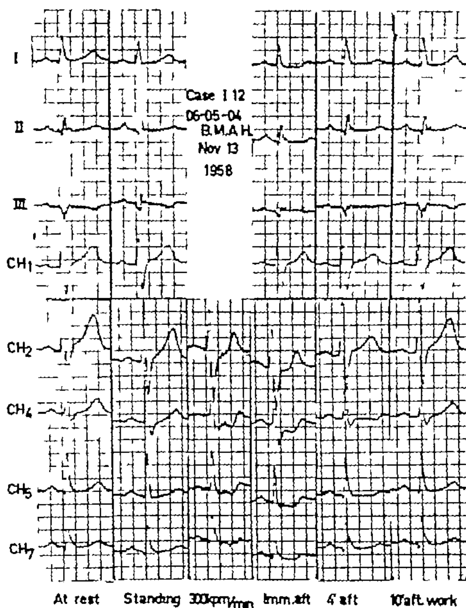

I
II
III
CH1
CH2
CH4
CH5
CH7
Case I 12
06-05-04
B.M.A.H.
Nov 13
1958
At rest
Standing
300kpm/min
Imm.aft
4' aft
10' aft. work

Fig. 24.

CHAPTER IV

THE SIGNIFICANCE OF VENTRICULAR PREMATURE BEATS OR RUNS OF VENTRICULAR TACHYCARDIA DEVELOPING DURING EXERCISE TESTS

Introduction and review of the literature

The appearance of ventricular premature beats (VES) is a very common occurrence, which most people have observed. It is, except under certain circumstances, a harmless condition, that may be influenced by different factors. The most common reaction when such a patient undergoes a physical work test with sufficient increase of the pulse rate, is the disappearance of the VES. This is apparently due to the fact that the ectopic focus, which emits the impulses to the VES, is blocked by the normal focus when this reaches a higher frequence.

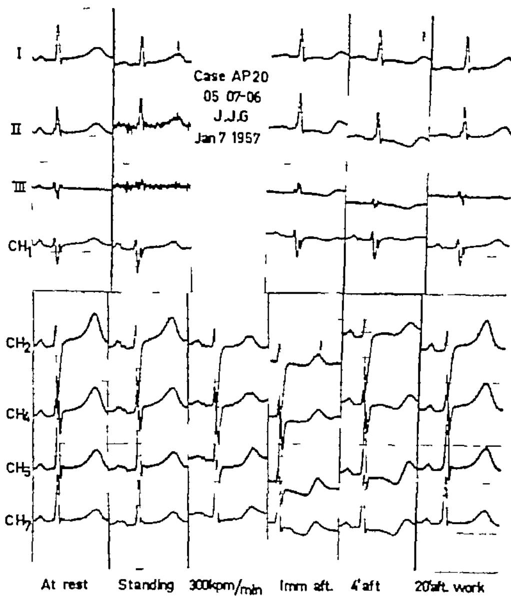
The condition is different, however when a normal rhythm at rest develops into an arrhythmia with more or less frequent VES during or after work. In this case, it may be presumed that there is a functional change in the myocardium varying with activity excitability oxygen supply or other factors.

According to several authors (1, 2, 3, 4) the appearance of premature beats after exercise is definitely abnormal, and particularly so if they are multifocal or in bigeminal rhythm.

As early as 19[illegible] [illegible] (1) stated in an investigation [illegible] with VES at rest, that the ma[illegible] [illegible] observed in rheumatic pa[illegible] [illegible] focal. He also found that in groups with myocardial affections a large percentage of VES is multifocal, whereas in groups not suffering from myocardial disease such multifocal premature beats are either absent or at least very rare.

In 1932 Goldhammer and Scherf (2) described a case of VES in bigeminal rhythm with anginal pains and S—T depressions in a patient after ascending a flight of stairs.

In 1935 Proger Minnich and Magendantz (6) published a report on a similar case. They also succeeded in showing that the abolition of the VES with quinidine increased the patient's working capacity without his feeling any pain. Similar results were published by Porter in 1948 (7). He also maintains that "A bigeminal rhythm after acute myocardial infarction may precede ventricular tachycardia and fibrillation, both in the experimental ligation of coronary artery and in acute coronary occlusion occurring in man. It is with these facts in mind that one feels justified in suggesting that the occurrence of frequent premature beats and especially a bigeminal ventricular rhythm during an attack of induced angina pectoris has grave prognostic significance." Porter considers that a



Case AP20
05 07-06
J.J.G
Jan 7 1957
I
II
III
CH1
CH2
CH4
CH5
CH7
At rest
Standing
300kpm/min
1mm aft.
4' aft
20' aft. work

Fig. 26

used in this study. Bengtsson (1956) (25) found that disturbances in rhythm were uncommon except during the first few minutes after the completion of the exercise.

In some recent studies, Master et al (1957) (27) and Mattingly et al (1954) (28) concluded that the appearance of premature beats after exercise was not a significant finding. According to Master et al. an increase in myocardial irritability may possibly be produced solely by the stretching that results from an increased stroke volume after exercise combined with the secretion of epinephrine, and does not necessarily reflect myocardial hypoxia. A similar conclusion is drawn by Lepeschkin and Surawicz (1958) (29) on the basis of their study of 243 cases where Master's technique was applied.

As it is apparantly of the greatest importance to disclose such an arrhythmia at as early a stage as possible, in order to prevent an attack of ventricular tachycardia, perhaps with ventricular fibrillation and a fatal outcome, an exercise test must include the possibility of Ecg recording also during and not only after work. The purpose of this study is to show the significance of such rhythm disturbances.

Method

The possibility of registering VES in an exercise test depends to a very great extent upon the method used. It is desirable that the Ecg recording should be performed throughout the test, but for practical reasons this is often impossible to achieve. An ordinary recording usually lasts between 10 and 15 seconds with a paper speed of 50 mm per second, which means, at a pulse frequency of 60 beats per minute, the registration of 10—15 beats.

Therefore in cases of arrhythmia the registration should be made at a lower paper speed, for instance 25 or 10 mm per second, in order to detect a periodical irregularity. In the present study these necessary conditions have been taken into consideration. The registration time and the speed mentioned were varied from case to case, depending upon the frequency and character of the arrhythmia.

When the Ecg records are entered on cards, representative parts of the Ecg are selected. The nurse who makes the Ecg recording is asked to describe what happens during the test, e. g. appearance and frequency of VES, the patient's subjective symptoms, such as tiredness, anginal pain or any other observations of interest.

The great importance of having the test made by an experienced person should be emphasized, as this not only increases the value of the test, but also reduces the risks for the patient.

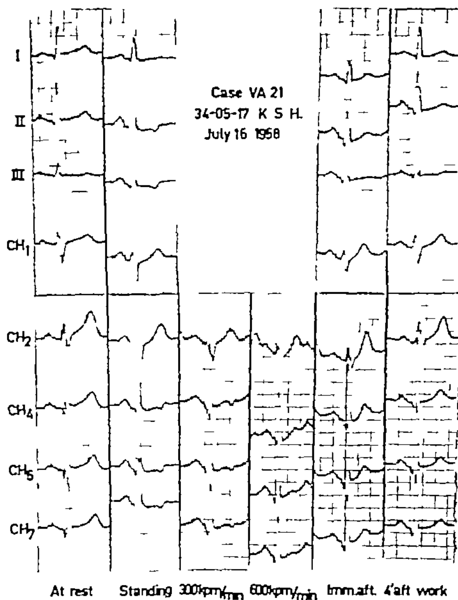

I
II
III
CH1
CH2
CH4
CH5
CH7
Case VA 21
34-05-17 K S H.
July 16 1958
At rest
Standing
300kpm/min
600kpm/min
Imm.aft.
4'aft work

Fig 27

3 Peptic ulcer anginal pains?
5 Angina pectoris.
7 Angina pectoris, Hypothyreosis, Diphteria.
10 Angina pectoris, Hypertension Diphteria.
11 Severe hypertension.
15 Angina pectoris.
16 Angina pectoris myocardial infarction peptic ulcer
21 Angina pectoris, Intermittent claudication.
24 Angina pectoris, Depressio mentis.

The first case (No. 6 Fig 30) in the age-group 23—39 years, was a 28 year-old waitress, without other heart trouble in two tests, however VES developed four minutes after work, but not during work. Another test made one year later showed quite normal results for the exercise test, except for atrial pacemaker shift. The physical working capacity (PWC) was normal in relation to the total amount of hemoglobin (THb) and the heart volume, in a prone position (HV) is somewhat large *in relation to the THb.*

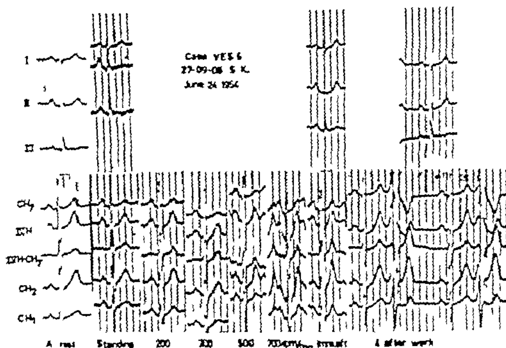


Fig 30

Case 9 wa a 39 y a old engineer with VES as th only ymptom The investigation show d a m H e larg HV in relation to the THb. The PWC could not be est mated, because the e r se test was *discontinued* at an

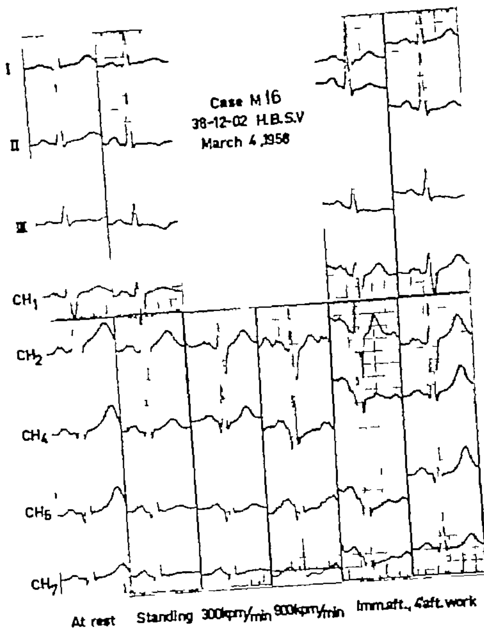

Case M 16
38-12-02 H.B.S.V
March 4, 1958
I
II
III
CH1
CH2
CH4
CH5
CH7
At rest
Standing
300kpm/min
900kpm/min
Imm.aft.
4'aft. work

Fig. 19.

mia. Both these tests were, however performed very carefully in view of the results of the first test. Four years later the patient died of an acute coronary disease after he had still been suffering from angina pectoris of an effort type

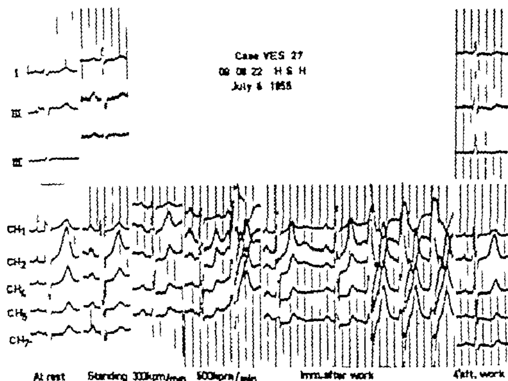


Fig. 3

The third patient, case 28 Fig. 32 a 52 year-old factory worker developed short runs of ventricular tachycardia during work, which still continued immediately after work, but then disappeared. The patient was quite free from heart symptoms he was admitted to the hospital to the investigation of a pulmonary silicosis. No S—T T depressions were observed during or after the test. A second investigation four years later which included also the determination of THb and HV showed quite normal conditions, except for the pulmonary disease and the patient was still quite free from heart symptoms.

for more than two to four minutes. Lepeschkin and Surawicz were unable to determine a sharp dividing line between these two groups in respect of the duration of the abnormality and the experience gained with the method used in the author's investigation appears to agree with their results.

On the basis of the results obtained in the present investigation an orthostatic Ecg test of sufficient duration may be an important aid in differentiating sympathicotonic from coronary Ecg changes. Evidently the average cases of coronary diseases differ from those with myocarditic or sympathicotonic Ecg changes. The last two groups seem then to be differentiated by studying the behaviour of the S—T and T interval during the different stages of the test

Conclusion

Three groups of cases have been studied both in orthostatic tests and during, and after exercise, by the method used in Karolinska sjukhuset. In all, the author investigated forty four cases with normal or almost normal Ecgs at rest which developed obvious changes in the S—T T intervals during a combined orthostatic and exercise test, with Ecg recordings during and after the test. The cases are divided into three groups according to the clinical diagnosis cases with ischemic heart diseases sympathicotonic Ecg changes and status post myocarditidem.

It seems possible, with the aid of a combined orthostatic and exercise test, to distinguish cases of ischemic heart disease from those with a sympathicotonic Ecg reaction and status post myocarditidem. The two latter groups may then be separated by studying the behaviour of the S—T and T changes during the different stages of the test.

One of the most typical features when distinguishing cases with ischemic heart disease from those of a myocarditic origin, seems to be the fact that the changes of the latter are predominantly localized to the T waves contrary to the S—T intervals in the former group.

References

a. *Bengtsson E.* Acta Med. Scand 54 5 956

b *Bengtsson, E.* Acta Med. Scand. 59 957

Bengtsson, G Nord. Med. 39 33 948

3. *Biorck, G* Am. Heart J 3 2689 946.

4. *Biorck G & Dalhamn, T* Cardiologia 7 366 950.

5 *Biörck G & Pannier R.* Nord. Med. 33 3 5 947

6 *Cosby R. S & Mayo, M* Am. J. Cardiology 31444 959.

7 *Durham, J R.* JAMA 5518 6 954.

8 *Einthoven W* Weiteres über das Elektrokardiogramm Arch. f. d. ges. Physiol. 5 71 908

9. *E ert, B* Cardiologia c6 938.

0. *Goldenberg, M and Rothberger J* Pflügers Arch. 39 56 937

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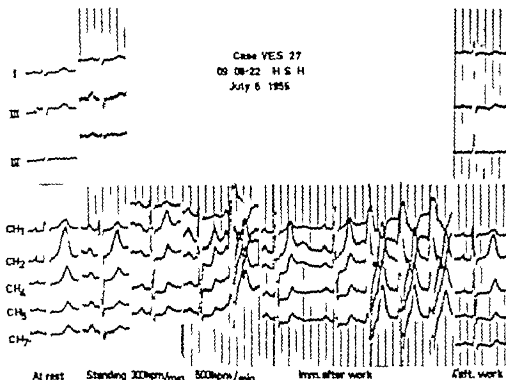


Fig. 3

The third patient, case 28 Fig. 32 a 5 year-old factory worker developed short runs of ventricular tachycardia du ng work which still continued mmediately after work but then d appeared The pat ent was quite free from h art s mptom he was admitted to th h p tal to th [illegible] st at on of a pulmonary silicosis. No S—T T depressions were observed during or after the test. A second investigation four years later which included also the determination of THb and HV showed quite normal conditions, except for the pulmonary disease and the patient was still quite free from heart symptoms.

53. *Smith J E.* J. Aviation Med. 470 1950.

54. *Strandell, T.:* Personal communication.

55. *Thomas, C. B* Bull. John Hopkins Hosp 89 181 95

56. *Twiss, A. & Sokolow M* Am. Heart J 31498 942.

57. *Wood F C., Wolferth, C. C. & Livezey M M* Arch. I t. Med. 47 339 931

58. *Wood P Mc Gregor M Magidson, O. and Whittaker W* Brit. Heart J 363 950.

59. *Yu, P N G Bruce R. A., Lovejoy L W J or and Mc Dowell, M E* Circulat on 3 368 1 95

60. *Y P N G & Soffer A* Ci culation 6 83 952.

61. *Åkesson, S.* Acta Med. Scand. Suppl. 5 946

62. *Åstrand I* Acta Physiolog Scand 49. Suppl. 69 1960.

The physical working capacity heart volume and total amount of hemoglobin in cases with VES developing during or after exercise

It was possible only in 13 cases to study the relationship between these factors, as described by Sjöstrand et al (14—21) The main reason for this was, that it proved impossible to estimate the above-mentioned factors in several cases, because the tests had to be discontinued at such an early stage, on account of the VES

The results of the thirteen cases investigated are given in figures 33—35

These figures show that the PWC is lower when compared not only with the values obtained from the THb but also with those from the HV

The lowest PWC in relation to THb is found in case 20 a 34 year-old man with attacks of supraventricular tachy cardia but a new determination made three months later yielded a more normal value, as is shown in Fig 33 The same applies to the PWC in rela tion to the HV

There are no cases with higher PWC when compared with the values obtained from the HV and only cases 3 and 19 fall within the normal variation.

In all cases but four the HV is larger when compared with the values obtained from the THb The highest value was that of case 17 a 23 year-old man with a complete atrioventricular block

larger number series of patients must be studied before final conclusions can be drawn

Other authors, including Master et al. (8) have asserted that the occurrence of arrhythmia after exercise was abnormal but in view of the method they employed it is very probable that they missed several cases of arrhythmia, as they had no Ecg recording during the performance of the exercise but only after its completion

The same method was mainly used when, in 1952 Mann and Burchell (9) found, in a study of 400 consecutive cases, 21 patients with VES after exercise 10 of these patients had premature beats also at rest, whereas for 11 patients, the changes occurred after the test. All these 11 cases had clinical signs of coronary insufficiency and the mean age was 52 years. Mann and Burchell stated in this investigation that when this abnormality was present before exercise and persisted or became more frequent after exercise, there was no evidence of coronary insufficiency in the majority of cases but coronary insufficiency was present in all cases where VES were precipitated by exercise.

In 1932 Wilson et al (10) described a clinical type of paroxysmal tachycardia of ventricular origin where the abnormal mechanism was induced by physical and mental stress. In the majority of cases there were no other signs of heart disease, but the patients were, nevertheless, seriously handicapped. In one of the cases studied, long paroxysms of ventricular tachycardia occurred, which were temporarily interrupted by short attacks of atrial paroxysmal tachycardia.

A similar case is described by Klakeg and Parkin (11) with atypical anginal pains and a brief episode of ventricular tachycardia registered immediately after exercise as well as other Ecg changes consisting of elevation of the RS T segment in the precordial lead V and V2. Similar cases are described by Mann and Burchell (9).

In most of these studies methods a. used which preclude the possibility of following the Ecg variations not only after but also during exercise this of course diminishes the value of the investigations.

In 1951 Yu et al (12) published a study of exercise tests conducted by the treadmill method, where precordial lead Ecgs were registered by a direct writing instrument during treadmill walking in this connection they also described VES in a case of arteriosclerotic and hypertensive heart disease In a group of patients with congenital heart disease of an undefined type, VES developed in two cases without significant change of RS—T segment or T waves.

Yu and Soffer published in 1952 (13) a study of Ecg changes during exercise in connection with a modified Master's two step test, which included Ecg recording at rest, during work, and in the early and late stages of recovery They asserted that, when VES appeared during exercise, they persisted in most cases up to the period of recovery

In his investigation of 125 healthy children and adults, where he employed, in principle, the same method as that

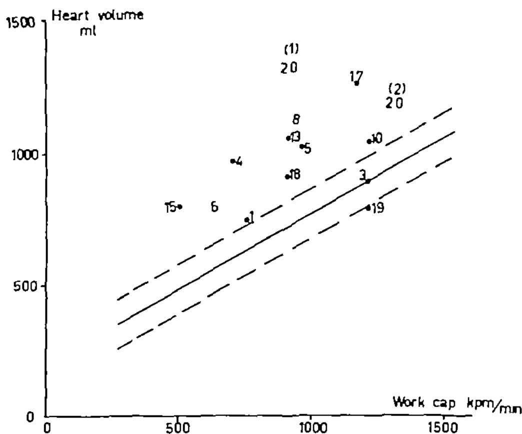


Fig 34 Heart volume (ordinate) in relation to physical working capacity (abscissa) For further explanation see Fig 33 The normal regression line equation y = 0.59 x + 90, Sy = 93, = 0.93

Material

The material consists of twenty seven cases with a regular rhythm at rest, but where the VES appear during or after work. Cases with digitalis have been excluded. There were three women and twenty four men. Their age varied from 23 to 72 years.

No conclusions about the frequence in the two sexes can be drawn because of the selection of the material.

The patients were clinically investi gated and, in most cases, blood volume total amount of hemoglobin, and heart volume, as defined by Sjöstrand et al (14—21) were determined as well as other data of significance for obtaining the clinical background to the mode of reaction.

For further data see table 23

Results

The significance of VES appearing during or after exercise

The patients have been divided into three age-groups, as shown in table 20, which also furnishes further data on the material.

TABLE 20

Symtoms and diseases in d fferent age groups

Group I 23—39 years

Case 6 Repeated or severe infections.
9 Healthy
13 Nervous symptoms.
17 Complete atrioventricular block.
18 Complete atrioventricular block.
19 Atrioventricular block with Wenckebach s periods.
20 Tachycardial attacks. Fainting.
25 Nervous symptoms, dizzi ness, dyspnoea, anginal pain.

Group II 40—54 years

Case 1 Peptic ulcer
4 Angina pectoris, Hyperten sion Diabetes mellitus.
8 Nervous symptoms, severe infections.
12 Hypertension severe infec tions.
14 Nervous symptoms, over strained businessman.
22 Angina pectoris, earlier myocardial infarction.
26 Angina pectoris. Mors 956 Myocardial infarction.
27 Angina pectoris. Mors 1960 Myocardial infarction.
28 Chronic, fibrous pulmonary disease (Silicosis pulm?) Diphteria.

Group III 55—72 years

Case 2 Myositis chron., Hyperten sion.

Discussion

The connection between VES appearing during or after exercise and coronary heart disease

As is emphasized by several authors coronary disease is a common cause of VES developing during or after exercise. Mann and Burchell (9) found, in a material of 400 consecutive cases, that coronary insufficiency was present in all cases in which VES were precipitated by exercise. The age of the individual patients was not reported however only the average age was given, 52 years for the eleven cases. If all the cases belonged to higher age-groups the result may be accepted but it cannot be true for younger persons, where the frequency of coronary diseases is much lower

The connection between VES and S—T T changes developing during or after exercise

When studying the eleven cases with angina pectoris and VES appearing during or after an exercise test, it is striking that in all cases but two the appearance of VES is combined with obvious S—T T depressions of the type that is common in coronary diseases. Of the two cases that diverges, No. 10, has as is pointed out elsewhere been tested only with low loads and it is likely that S—T T changes might have appeared if the test had not been discontinued at such an early stage because of the ventricular bigeminal rhythm

Obvious S—T T depressions during the exercise test with clinical signs of angina pectoris, were only observed in two cases. The first patient, case 12 a 49 year-old man with slight hyper tension had been treated with digitalis until one month before the test and, as is shown by Nordström-Öhrberg (26) the effect of digitalis on the Ecg may persist even longer than this, possibly this may be the explanation. The second patient case 13 a 37 year-old man with nervous trouble, exhibited, when in an upright position S—T T depressions of the type which may be a sign of vegetative imbalance.

As is shown in table 20 the first age group comprises eight cases, of which only three have obvious signs of heart disease, Nos. 17 18 and 19. With the exception of No. 25 in no case was there either any suspicion of coronary disease or any S—T T depressions of the type described as signs of coronary disease.

A differing opinion about the pathological meaning of premature beats (of not defined origin) was published by Mattingly et al. (1954) (28) Master et al (1957) (27) and Lepeschkin and Surawicz (1958) (29) they found that premature beats appearing after exercise were of little pathological importance

This seems to be only partly in agreement with the present study A criterium for a pathological significance of premature beats appearing during or after exercise is that they are combined

early stage on account of the frequent VES.

Case 13 was a 37 year-old factory worker without any special diseases or symptoms of interest but, like other members of his family he was nervous. In an upright position, his Ecg revealed a pronounced depression of the T waves this depression was of a sympathicotonic type (Holmgren et al. 1959) (22) The T waves became more positive during and after work, which does not appear to indicate coronary disease.

Three cases in this group 17 18 and 19 show already at rest, pathological Ecg changes localized in the atrioventricular conduction system; the cause of the premature beats may be due to this condition.

Case 20 was a 34 year-old lumberman without previous diseases or symptoms of interest. On admission to hospital the only symptoms he displayed were attacks of tachycardia and fainting. The investigations revealed only an abnormal Ecg during exercise A second exercise test, carried out $2^1/_2$ months later yielded quite normal results. He then showed a very good PWC had no further attacks of tachycardia or fainting, and felt quite healthy

Case 25 a 31 year-old taxi driver has been treated as an outpatient since several years he has exhibited different psychosomatic symptoms, but there has been no evidence of organic heart diseases or other diseases of interest.

To sum up it may be stated that there are no unequivocal signs of organic heart disease in this group, except the three cases with A—V block, and case 20, who seems to have had a temporary disturbance

In the age-group 40 54 years, there were symptoms of both organic and psychosomatic diseases, e g peptic ulcer Three cases of earlier myocardial infarction belong to this group and also case of earlier diphteria, which has tendency to cause persistent arrhythmia according to Hiemola (23 24) and Bengtsson (25)

Three patients in this group cases 14 27 and 28 revealed runs of ventricular tachycardia during and after exercise Case 14 a 47 year-old overstrained manager without any heart symptoms, but sometimes with irregular pulse observed during physical work, showed frequent VES during the first and third test. The second test showed VES already at rest, which disappeared when in an upright position, and returned during exercise. The fourth test showed runs of ventricular tachycardia during work these symptoms ceased immediately after the work was discontinued. No S—T T depressions were observed and the patient had no pain during or after the test. It should be pointed out that the patient was under treatment with quinidine when the last test was performed.

The second patient, case 27 a 46-year-old engineer with a history of typical angina pectoris, showed (see Fig. 31), pronounced S—T T depressions and single VES during exercise and immediately after the exercise had stopped there followed a period of ventricular tachycardia. Two later tests showed obvious S—T T depressions of the same type as before but no arrhyth

In spite of the small number of cases, the results of this investigation seem to confirm however the conclusion based on the study of VES developing during or after work, that the decisive factor is whether or not the rhythm disturbance is connected with S—T T depressions.

Conclusion

In a study of twenty seven adults with ventricular premature beats or runs of ventricular tachycardia developing during or after exercise it was shown that there were two different groups to consider One consisting of young persons without heart symptoms or other diseases of interest, where the arrhythmia appeared at first on heavy loads and seemed to be an effect of physiological changes. In these cases there was no evident connection with heart diseases, particularly ischemic heart diseases, contrary to the other group. The latter comprised older patients who exhibited ventricular arrhythmias already on low loads, often combined with angina pectoris or other symptoms from the circulatory system and this was frequently accompanied by other signs of heart diseases, su h as S—T T changes of the type found in ischemic heart diseases.

References

Blanc G A ch. d. mal d coeu 44 846 195

2 *Goldhammer S and Scherf D* Ztschr f klin. Med 34 93

3 *Scherf D and Goldhammer T* Ztschr f klin. Med. 24 1 933

4. *Scherf D and Schaffer A I* Am Heart J 43:9 7 952.

5 *D'I say S* Am. J Med Sc. 74:461 9 7

6 *Pr ger S H Muensch W R and H gendan H* Am Heart J 0-5 935

7 *Porter W B* Am J Med. Sc. 6 509 948

8 *Master A. M Friedma R d Dack S* Am. Heart J 24 777 95

9 *Mann R. H and Bur hell H B* Proc Staff Meet May Cl 7 383 95

u *lson F N W shart S W M lcod A G and Barker P S* Am Heart J 55 93

1 *Klakeg, C. H and P Hu, T W* Proc. Staff Meet., Mayo Clin 4197 954.

12 *Yu P N G Bruce R. A Lovejoy L W jr and Mc Dowell, M E* Circulation 3 368 95

3 *Y P N G and Soffer A.* Cir ulat on 6 183 952.

4. *Holmgren A Jonsson B Levander M Linderholm, H Sjost and T and Strom, G* Acta Med. cand. 153:4 3 957

5 *Sjost and T* Acta Physiolog. Scand'na 61 948

16. *Sjost and T* Acta Physiolog. Scandi a 6121 948.

7 *Ca lsten A Holmgren A., Linroth K Sjöstrand T and Ström, G* Acta Physiolog. Scandina 31 6 954.

8 *Linderholm, H and Sjöst and T* Acta Physiolog. Scandina 37:2:401 956

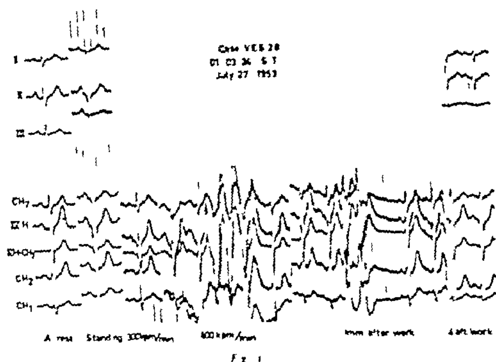


Fig 1

In the third age-group 55 72 years all the cases showed symptoms of evident organic diseases nvolving the heart. The most striking example here case 16 a 56 year-old engineer who, ten lays after an exercise test, developed a typical myocardial infarction. The exercise test showed pronounced S—T and T depressions and VES in bigeminal rhythm.

The combination of VES appearing during or after exercise and angina pectoris

The group consist ng of patients with typical angina pectoris, comprised ele ven cases, 4 5 7 10, 15 16 21 24 25 26 and 27

When studying the S T and T ntervals during and after work obvious depressions were found in cases 4 5 15 16 21 24 25 26 and 27 In case 7 the VES derive from more than one focus, which is generally accepted as a pathologic sign. In case 10 the absence of S T T depressions may be due the fact that the exercise test was disconti nued already after the second load, because of VES in bigeminal rhythm. In case 21 repeated Ecg recordings revealed S—T T depressions already at rest, as a sign of coronary disease which agreed well with his typical angina pec toris.

CHAPTER V

ELECTROCARDIOGRAPHIC STUDIES OF CASES WHERE BUNDLE-BRANCH BLOCK DEVELOPS DURING EXERCISE TESTS

Introduction and literature review

Bundle-branch block (BBB) is defined as a condition where the normal intraventricular conduction is delayed because of a change in the bundle of His.

BBB may be localized in the right or left branch (of these the latter localization seems to be the more common) or in both branches. This depends upon the kind, degree and localization of the injury The Ecg changes concist of an increased duration of the QRS complex and an altered configuration. It is fairly generally accepted that the term BBB should be applied only if the QRS time exceeds 0.12 seconds otherwise the terms incomplete BBB or only intraventricular conduction disturbance are used.

The cause of permanent BBB may be a congenital disturbance or an injury produced by a myocardial infarction or myocarditis (a diagnosis which however is often difficult to establish) or the result of a left or right ventricular hypertrophy (1 2)

According to Eichert (3) once BBB is established, it tends to become permanent but in those cases where it is only transient it may prove very difficult to induce a chang in conduction and "such cases, n which the BBB only occurs when the cardiac rate is rapid are extremely rare" Eichert investigated also a case where BBB developed during exercise, whereas the Ecg at rest and after work was normal. He studied as well treatment with different drugs that increase the pulse frequency The exercise performed is not defined but the patient's Ecg reaction was followed in a cardioscope. It was possible, in this case, to reproduce the BBB both during exercise and with drugs such as amyle nitrite and atropine, if the pulse rate only exceeded a certain level. At the moment when the BBB appeared, the patient had a feeling of palpitation. Segers and Denolin (4) report a case of BBB which developed during an exercise test (not defined) and disappeared with decreasing pulse rate after the test. The patient had then a bradycardia of 55 beats per minute at rest, and when the pulse rate subsequently increased to 80 the BBB became permanent.

Comeau et al. (5) stated in an investigation of paroxysmal BBB that in the "routine records of their cases was there no constant correlation between cardiac rate and the degree of intraventricular conduction"

Twiss and Sokolow (6) are of the

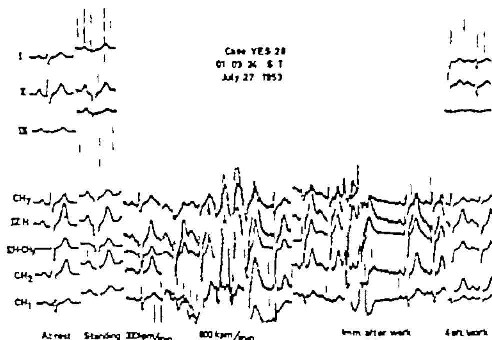


Fig. 32.

In the third age-group 55—72 years, all the cases showed symptoms of evident organic diseases involving the heart. The most striking example here is case 16 a 56-year-old engineer who ten days after an exercise test, developed a typical myocardial infarction. The exercise test showed pronounced S—T and T depressions and VES in bigeminal rhythm

The combination of VES appearing during or after exercise and angina pectoris

The group consisting of patients with typical angina pectoris, comprised eleven cases, 4 5 7 10 15 16 21 24 25 26 and 27

When studying the S—T and T intervals during and after work obvious depressions were found in cases 4 5 15 16 21 24 25 26 and 27 In case 7 the VES derive from more than one focus, which is generally accepted as a pathologic sign In case 10 the absence of S—T T depressions may be due the fact that the exercise test was discontinued already after the second load, because of VES in bigeminal rhythm. In case 21 repeated Ecg recordings revealed S—T T depressions already at rest, as a sign of coronary disease, which agreed well with his typical angina pectoris.

gradual alteration of intraventricular conduction seem to be rare

It is a well known fact that abrupt alterations in the intraventricular conduction may produce subjective symptoms.

Material and methods

The material consists of nine cases investigated in the hospital.

The age limits were 31 and 62 years.

The sex distribution shows two women and seven men.

The conduction disturbance was localized in the left bundle in seven cases, and in the right in two cases.

The cases have been studied with Ecg during orthostatic and exercise tests, in accordance with the method, *previously* mentioned, which is used in the hospital. Some of them were studied several times and in three cases we succeeded in registering the alteration during continous Ecg recording with a low paper-speed. In the other cases, the change occurred between two Ecg recordings, consequently *the pulse rate at the moment the alteration took place, could not be exactly determined.*

The cases are described in table 24

Results

R—R intervals and critical levels

Table 24 shows the exact R—R time at the moment when the BBB appeared in the three cases where the change was recorded during continous Ecg recording. It is noticeable that "the critical level is not a fixed value when *comparing* the R—R intervals *during which* the BBB appears, with those *obtained when it disappears during decreasing* pulse rate. Also in case 2 the interval, during which the BBB disappears, is dist[illegible] [illegible]horte than that durin[illegible] which [illegible] appears

"The [illegible] al l[illegible] [illegible]s not appear to be a [illegible] d[illegible] [illegible]h patient when the [illegible] [illegible]ne time. In case 1 [illegible] R R value betw[illegible] 4 [illegible] the first tw[illegible] [illegible] seconds in the third test, i. e. at a higher pulse rate. Corresponding values for the disappearance are 0.50—0.66 seconds for the first two tests and between 0.35 and 0.55 seconds in the third test. The interval between the three tests was seven months, and no clinical signs of heart disease or other symptoms of interest have appeared in the meantime. The last time the heart volume was measured it was *normal* as compared with the value *obtained* from the total *amount* of hemoglobin.

In case 2 the R—R time is also shorter in the second test with an interval of two years between the two tests. A clinical improvement had taken place during this time.

In case 10 there is also a slight

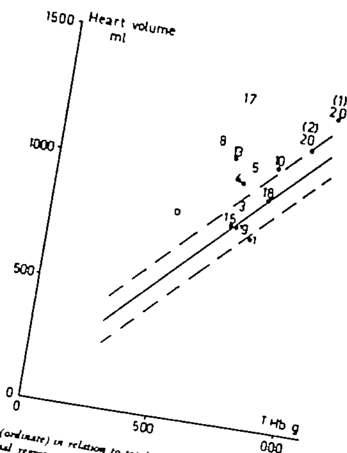


Fig. 33. Heart volume (ordinate) in relation to total amount of hemoglobin (abscissa). Straight line represents the normal regression line obtained from determinations in 58 healthy men, women and children (Holmgren et al. 1957 (4)), with the equation $y =$ [illegible] $x + 64$, $Sy =$ 93, [illegible] = 93. Dotted lines indicate variation ± one standard error of estimate (Sy). The numeral near the points on the diagram represent the case. Case 20 was investigated twice as shown in the diagram.

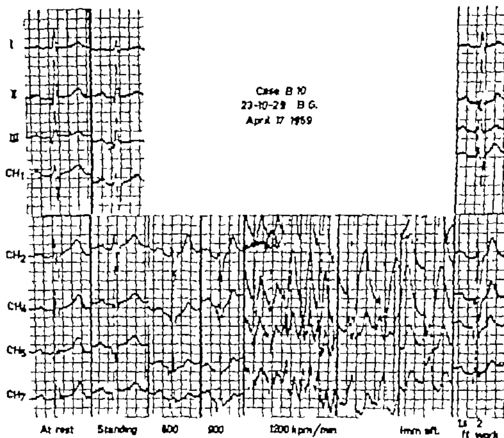
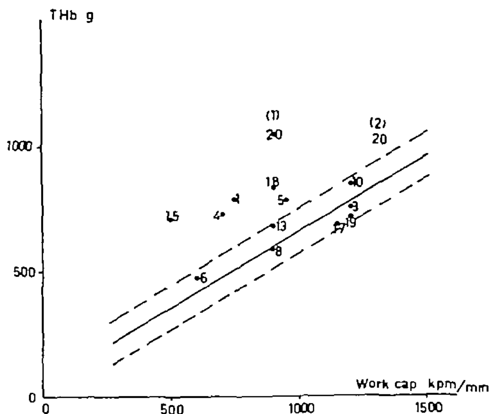


Fig 36. The Ecg is ecorded at pape -speed of 5 mm/sec xcept during the first recording under 00 kpm/min when the paper-speed is 25 mm/sec

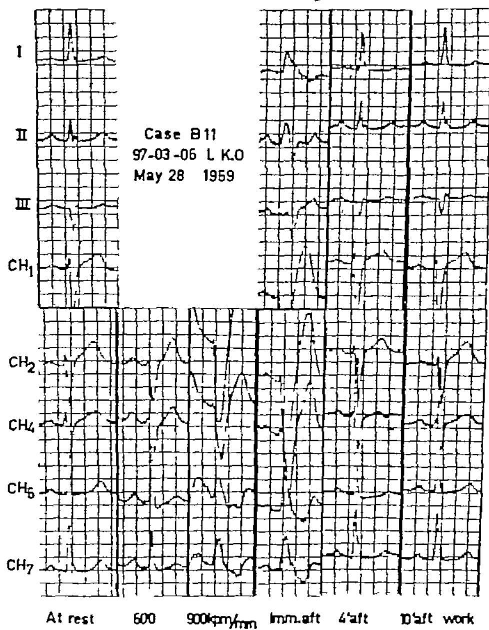
In case 10, (Fig 36) the second exercise test revealed a left BBB devel oping under the same load as was used in the first test which was carried out about three months earlier Under a load of 1200 kpm/min. and a pulse rate of 176 per minute, the patient looked pale and had a feeling of discomfort, when cor tinuous E g recording showed a prompt change to a left BBB In a recumbent position after the test, it was still present, but d sappear d together with his subjecti sympt ms 1 /s– 2 minutes later

Under a load of 1200 kpm/min case 14 showed, after some beats of varying intraventricular conduction an altera tion to a left BBB after a pulse rate of between 160 and 190. When in a recum bent position it still remained, imme diately after work at a pulse rate of about 150 but disappeared at a pulse rate of 115 after about four minutes test.

Case 15 had been tested twice before in 1951 and 1956 Both these investi gations showed normal intraventricular conduction but the first time the pulse



F g 35 Total amount f hemoglobin (ordinate) in relation t physical working capacity (abscissa). For further xplanation see F g 33 The normal regre sion lin equation y = 0.54 x + 60, Sy = 88 = 0.93



I
II
III
CH1
CH2
CH4
CH6
CH7
Case B11
97-03-06 L K.O
May 28 1959
At rest
600
900kpm/min
Imm.aft
4'aft
10'aft work

Fig 37

with S—T T depressions. The conclusions of the authors previously mentioned appear however to be quite satisfactory in respect of cases where premature beats, appearing during or after exercise are not combined with S—T T changes.

Thus, it may be stated that in this investigation the appearance of VES during or after exercise in older persons with angina pectoris, is almost invariably followed by S—T T depressions of the type described in coronary diseases. In these age-groups the results fit well with those of Mann and Burchell, but this does not apply to younger persons.

It seems also evident that VES appearing during or after work, without corresponding S—T T depressions, might be of less gravity but this necessitates the test being conducted to a level where the S—T T changes can be expected to appear. This is often a difficult decision to make in view of the risk of producing more severe arrhythmias.

Heart volume total amount of hemoglobin and physical working capacity in cases with VES appearing during or after exercise

It is interesting to note that the values of the PWC, when compared to those obtained from the HV and the THb are lower in most cases, as is seen in figures 33—35. Owing to the difficulty of determining the PWC in cases of arrhythmia, it has been impossible to observe how these factors vary in the three age groups a comparison which would have been of the greatest interest.

The influence of other factors on the appearance of VES during or after exercise

It is interesting to note, in connection with this material that three patients had had diphteria but as two of them have now a typical angina pectoris, it is difficult to draw any conclusions about the significance of this.

The significance of ventricular tachycardia developing during or after exercise

As has been mentioned in the introduction several authors reported cases of ventricular tachycardia developing during exercise, and, as emphasized by Wilson et al. (10) most of the cases showed no other signs of heart disease.

Case 4 had, about one year before the first test, a fever of rather long duration with palpitation and general weakness, which seems to agree well with acute rheumatic fever

Exercise test

Case 1 has been investigated four times between 1949 and 1957 The first test showed normal intraventricular conduction in spite of such a heavy load as 1500 kpm/min, at a pulse rate of 152 per minute. The two following tests showed left BBB under the loads and at the pulse rates described in table 24

This seems to be a boarder line case when the BBB appears, the loads are lower than but the pulse rates about the same as, in the first group In the other cases the alteration already appears when rather low loads are applied and with pulse rates as shown in table 24

Conclusion

The qualities in common for these six cases were

1 The average age is higher than in the first group between 38 and 62 years.
2. The BBB appears already at rather light loads.
3 The patients have signs of heart or other circulatory diseases or a case history with repeated infections.

Discussion

In most of the cases studied in this investigation no "critical level" appears to exist the condition seems to be very variable, possibly changing with insufficient oxygen supply during exercise.

It has been shown that in young and otherwise healthy persons, BBB may develop under heavy loads at high pulse rates, but this may be in keeping with the explanation given by Master (1957) (24), among other investigators, of the cause of premature beats developing during and after exercise in presumably healthy young persons after heavy work.

An important point with regard to the material studied here is, that at least five of the six cases in the second group showed signs of organic heart diseases in their history and typical angina pectoris was indicated in four of these cases.

In view of the available knowledge about the oxygen supply of the bundle of His and its branches from the left descending coronary artery it is not surprising that the patients in the second group demonstrated both angina pectoris and transient BBB even during mild forms of exercise

20. *Kjellberg, S. R., Rudhe, U. and Sjostrand, T.* Acta Radiol. 3 3 949

1 *Kjellberg, S. R., Rudhe, U. and Sjost d, T.* Acta Radiol. 3 3 1949

22. *Holmgren, A., Jonsson, B., Levander, M., Linderholm, H., Sjostrand, T. and S om, G.* Acta Med. Scand. 65 59 959

23 Akemola, E., Acta Soc. Med. Fenn. "Duodecim" 3 59 932.

24. *Klemola, E.* A ch. f. K eisl afforsch 3 6 943.

9 *Wiklander, O.* Acta Chir. Scand. Suppl. 8 956

5 *Bengtsson, E.* Acta Med. Scand. 54 8 956

6 *S ndstrom-Ohlberg, G.* Personal communication

7 *Master, A. M., Field, L. E. and Donoso, E.* New York State J. Med. 57 5 957

8 *Mattingly, T. W., Fancher, P. S., Bauer, F. L. and Robb, G. P.* Army Medical Service Graduate School Research Report, —54, Sept., 954, Washington, D. C. Walter Reed Army Medical Center

9 *Lepeschkin, E. and Surawicz, B.* New E. J. J. f. Med. 58 5 958

CHAPTER VI

THE EFFECT OF EXERCISE ON THE ELECTROCARDIOGRAM OF PREEXCITATION

Introduction

Since Wolff, Parkinson and White in 1930 (1) described a syndrome of short PR interval with abnormal QRS-complexes and attacks of paroxysmal tachycardia (P.T.), this phenomenon has been studied by several authors. There is however some disagreement as to its denomination [illegible] and in accordance with Öhnell (2, 3) the author prefers to call the syndrome with the ECG changes previously mentioned and attacks of P.T. the "Wolff-Parkinson-White" syndrome or W.P.W. syndrome, whereas the physiological phenomenon which [illegible] called preexcitation (P.E.) [illegible] the excitation wave from the atria does not show the normal delay in the atrioventricular node. The ECG picture then shows an initial slow phase in the beginning of the QRS complex, which on account of its shape is called delta wave.

According to [illegible] Wood (4) and other authors an abnormal [illegible] Prinzmetal et al. [illegible] ways by thermical, chemical and mechanical excitation of special portions of the heart. They also proved that P.E. complexes could not be produced after the bundle of His had been cut. A premature ventricular excitation wave presupposes that the normal conducting system is intact. They considered the syndrome to be a physiological rather than an anatomical disturbance; this seems also to be most in keeping with the author's experience as to the variability of P.E. However some other authors consider that P.E. cannot be explained only by Prinzmetal's theory because the conduction fibres react like a syncytium and that different path-ways in such a syncytium are impossible.

To conclude, it appears evident from the literature on the subject that this problem has not yet been satisfactorily solved and Prinzmetal et al. (5) declare that "Until more information concerning the normal conducting system is known, the true nature of ventricular aberration in the anomalous [illegible] W.P.W. syndrome and other similar disorders will be purely speculative."

opinion, in respect of the criteria of a positive exercise test with Ecg recording after but not during exercise that the development of BBB as well as of S T depressions is considered abnormal in cases of angina pectoris.

Feil and Brofman (7) found, when using Master's method in an investigation of 56 patients with BBB of different types, two cases of BBB after work. Unfortunately these were not studied more closely as the investigation was restricted to those cases where the BBB was present already at rest. They stated also that "there is little reference to the effect of exercise on the Ecg of BBB either in the normal person or in the patient during angina of exercise or of anoxemia"

The appearance of BBB usually right sided, has been observed in attacks of angina pectoris (6 8) The same has been seen after exercise (6 9) in patients with coronary artery disease.

No case of complete or incomplete BBB appearing during or after exercise was found by Bengtsson (1957) (10) in an investigation comprising 125 healthy children and adults, where principally the same method was used as that employed in this study

The connection between pulse rate and BBB appearing during or after exercise has been studied, among other investigators, by Vesell (1941) (11). He stated that intraventricular conduction during the 40 — to 50-year span of adult life is remarkably constant and, in the absence of heart disease, even considerable increases of the heart rate do not influence the contour of this complex.

Decreased circulation in the bundle of His and its branches is according to Vesell a rather common result of coronary diseases, probably depending upon the fact that this region has its blood supply from the left descending coronary artery and a BBB is often a sign of this.

Carter and Dieuaide (1923) (12) asserted that, with regard to the function of the atrioventricular conduction system a few intact fibres may under favourable circumstances serve to carry on the process normally while some subtle local circulatory deficiency or a temporary increase in vagal action may result in failure of the few remaining fibres to function

Erlanger (1924) (13) considered that restitution of the bundles of His, when once destroyed probably does not occur Therefore any recovery of function seems to be due to physiological alterations.

Such factors influencing conduction are lowered oxygen tension glucose, digitalis, quinidine, morphine displaced electrolyte balance local lactic acid excess and changes in the cardiac rate (14 15 16 17 18 and 19).

Furthermore, Vesell stresses that changes in position or exercise may expose a transient BBB, perhaps as a sign of coronary disease.

Some authors (20, 21 22 and 23) have pointed out that there is often a critical pulse rate connected with the appearance of the changes in conduction in cases of transient BBB but, according to Vesell this is not the most common condition and cases with the

tive, however in all three cases. Each patient showed a change in the T wave in the precordial lead.

The material studied by Wolff and White (8) consisted of 40 cases ten of these were investigated with exercise tests, but the method was not defined. In eight cases there was no effect on the Ecg in one normalization was achieved, and in another there was a change into atrioventricular nodal rhythm.

It seems to be very difficult to draw any conclusions from the findings so far reported. In order to elucidate the problem, an investigation was carried out where Ecgs were made during the exercise tests given according to the Sjöstrand—Wahlund technique Here Ecgs were recorded not only during, but also after the exercise this does not appear to have been previously described in the relevant literature.

Material

The author s material consisted of 35 cases where P.E. was established by examination in the hospital. Seven of these were excluded because of the difficulties of making a thorough exa mination exclude cases with cardiotropic pharmaca and other factors of interest.

No conclusions can be drawn about the sex distribution of the material because of the selection made. The preponderance of men may at least partly be ascribed to the fact that the hospital has a special military out ward.

Other details of interest are given in a short case report, table 25

Results

The Ecg changes in connection with exercise tests

P E may appear in three different ways

1 No P E at est, P E appears dur ng work

2. P.E. a [illegible] pears during work and re [illegible]

3 P E is not affected by the exercise test.

The distribution of the material in these three groups is shown in table 21 and Fig 39 It will be seen that most cases belong to the third group. Least common are those placed in the first group (two cases) These two patients were the oldest in the material their age was 51 and 56 respectively

alteration of the "critical level" but the difference is too small to allow of any conclusions being drawn.

Since the Ecg recording was not continued throughout the entire test, it has not been possible to establish whether the alterations appeared suddenly or were preceded by some beats whose configuration was gradually changing except in the three cases described. In two patients, cases 2 and 14 there is a gradual alteration in the shape of the QRS complex when the BBB appears, but not when it disappears.

Comparison of clinical signs and exercise tests

The cases have been divided into two groups, according to the presence of clinical signs of heart diseases. The first group consists of cases 0 14 and 15 which had no clinical heart symptoms of interest, and the second of the remaining six cases with clinical signs of heart diseases.

The first group

The age of the patients in this group was 36 42 and 31 years

Case 10 had been a middle distance runner and plays tennis regularly without any subjective symptoms. The cause of the first investigation was a diffuse feeling in the chest during psychical stress.

Case 14 is an airline pilot without any symptoms, where the Ecg was taken as a routine control. He has no earlier history of diseases of interest, and a new exercise test, conducted about a month later showed a quite normal Ecg, although the last test was performed under the same load 1200 kpm/min.

Case 15 is a 35 year-old medical student without any clinical signs of heart disease but a systolic murmur over the third left intercostal space of the sixth degree, who had earlier been heart catheterized, when a ventricular septal defect with a small left to right shunt was found; this had a very slight effect on the circulation.

Exercise test

In addition to the data given in table 24, the following facts may be pointed out:

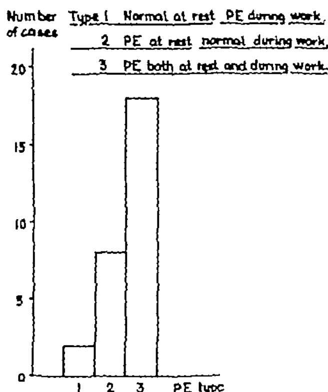


Fig. 39. Schematic presentation of the frequency of the three different reaction types ("PE types") during exercise tests.

As regards the constant character of the changes, case 12 Fig. 41 that showed a pronounced variability may be taken as an example. Many Ecgs at rest showed some times normal excitation, and at other times P.E. in every third to sixth beat and again on other occasions P.E. was constant. During exercise test normal excitation is found at rest and in a standing position, but during work at first single P.E. beats occur then three to four P.E. complexes in series, followed by normal beats.

rate was only about 140 per minute under 1200 kpm/min and the second time, 160 under 900 kpm/min The actual investigation revealed a left BBB under a load of 1200 kpm/min at a pulse rate of 176 The patient had an undefinitable feeling at the time when the BBB was observed The BBB disappeared between two Ecg recordings, made in a recumbent position, immediately after the work had stopped.

Conclusion

The qualities in common for these three cases were

1. The low age between 31 and 42 years.
2. The BBB appears at first under heavy loads.
3. There are no obvious clinical signs of heart diseases.

The second group

Case 1 had previously had throat and intestinal infections and had been tonsillectomized because of the repeated throat infections. On several occasions he had had attacks of palpitation, particularly after hard physical and mental work

Cases 2 6 11 and 13 have a typical case history of angina pectoris case 2 had suffered besides from poliomyelitis, and case 6 from a supposed Cushing's disease Cases 2, 4 6 and 11 had more or less increased blood pressure.

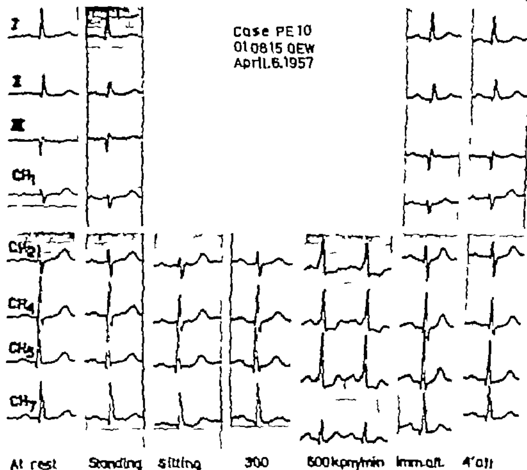


Fig. 40.

Do similar changes also appear in young persons with P.E., where ischemic heart changes may be excluded, i. e. in group 1?

If we compare the Ecg reactions of these cases in respect of the S—T and T intervals, we shall find that nine (1, 9, 13, 17, 22, 31, 32, 33 and 34) of the fourteen cases in this group showed pronounced plateau shaped depressions or inversions as strongly marked not only as those in the third group but also as the ones found in cases of grave coronary disease with typical angina pectoris.

Case 20 may be taken as an example.

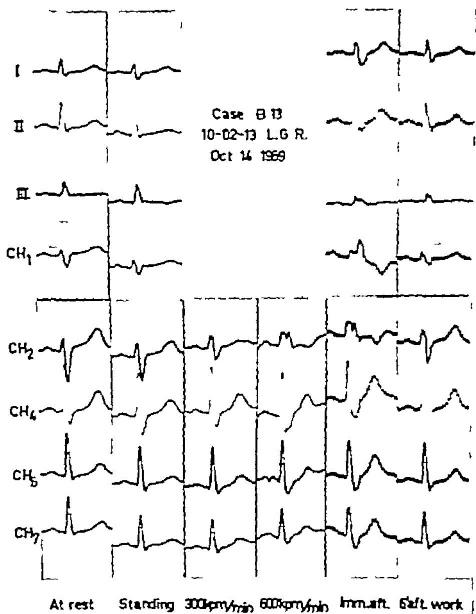

Case B 13
10-02-13 L.G R.
Oct 14 1969
I
II
III
CH1
CH2
CH4
CH5
CH7
At rest
Standing
300kpm/min
600kpm/min
Imm.aft.
6'aft. work

Fig 35

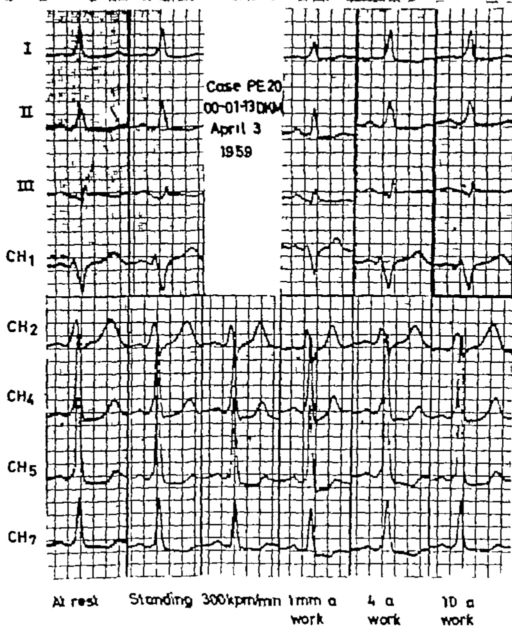

I
II
III
CH1
CH2
CH4
CH5
CH7
Case PE 20
00-01-13 DKM
April 3
1959
At rest
Standing
300 kpm/min
1 mm a work
4 a work
10 a work

Fig. 41

Conclusion

Out of nine cases that developed BBB during exercise two groups could be distinguished one consisting of younger persons who developed BBB only under heavy loads and at high pulse rates, and whose history showed no record of previous heart or other diseases of interest and the other comprising older persons with angina pectoris or other diseases involving the heart, where BBB develops even under light loads. The author's opinion is, that the first group has little pathologic significance contrary to the other group, where it appears that coronary artery diseases may play an important role

References

Lepeschkin E Modern Electrocardiography Vol. The Williams & Wilkins Co, Baltimore 95

Goldman M J Principles of Clinical Electrocardiography Lange Medical Publications, Los Altos, California, 956

3 *Eichert H* Am. Heart J 3 1 946

4 *Segers M and Denolin, H* Arch d Mal d Coeur 4) 947

5 *Comeau R J Hamilton J and White P D* Am Heart J 5 76 938

6 *Tuo A and Sokolow M* Am Heart J 3 498 94

7 *Feil H and Brofman B L* Am Heart J 45 66 953

8 *Bousfield G* Angina pectoris Lancet 45 948

9 *Kienle F* Das Belastungs-elektrokardiogramm und die Stufen-Ekg. Leipzig 946 Georg Thieme

Bengtsson, E Acta Med Scand 154 5 956

Wolf H Am J Med Sc 20 98 94

Carter E P and Dieuaide F R Bull John Hopkins Hosp 44 93

3 *Levy R L* Mechanism and Graphic Registration of the Heart Beat, 3d ed London, Shaw and Sons p 77 924

4 *Fisk B W* Arch Int Med 45 8 4 930

5 *Moore A S and Stewart H J* Am Heart J 5 469 93

6 *Hamburger W W* Med Clin North Amer 5 343 9 9

Levy R L Arch Int Med 5 45 9

8 *Oeconomopoulos D and Dimitriadis* Arch d mal d coeur 4 5 9 9

9 *Lydén A* Svensk Läkartidning 57 878 960

Herrmann G and Ashman R Am Heart J 6 375 93

Katz L N Hamburger W W and Rosenfeld S H Am Heart J 7 753 93

Sundstroem, A Acta Med Scand 67 335 9 7

3 *Wilson F N* Arch Int Med 6 008 9 5

4 *Master A M Field L E and Donoso E* New York State J Med 57 103 95

The heart volume and the total amount of hemoglobin in cases with P E

In prone position, the heart volume (HV) is correlated to the total amount of hemoglobin (THb) in accordance with the principles applied in this hospital. This is shown in figure 44. For different reasons it was possible to investigate only nineteen of the cases by this method.

Etiology

P.E. seems to be mainly of two types congenital and aquired.

In the latter case several factors have been considered. Lepeschkin has summarized the etiologic factors (6)

He states that the WPW syndrome is found in 60—70 per cent of cases with objective normal hearts.

In about 19 per cent, rheumatic fever was suspected to be the cause and in 10 per cent, various other infectious diseases were found.

Myocardial infarction and other symptoms of coronary sclerosis were observed in 23 per cent and hypertension in 13 per cent of the cases.

Hyperthyroidism was found in 6 per cent, ("but actually seems to be more common") and ntoxication with carbon monoxide and other gases was recorded in individual cases.

Jervell (7) describes a 37 year-old patient with toxic goitre who displayed at times regular P.E. patterns, and at other times P.E. in every second complex. The Ecg, as well as the basal metabolic rate was normalized after surgical treatment and iodine.

Wolff and White (8) reported a material of 41 cases, five of which had thyroid diseases. One patient suffered from thyrotoxicosis and another from thyroiditis. The other three cases were not specified.

Strong (9) described a case of WPW syndrome in a thyrotoxic patient whose Ecg was quite normalized after medical treatment with thiouracil similar cases are described by Lamb (21) Master (22) Mihálkovicz & Kovács (23) and Willis & Carryer (24)

Doumer and Merlen (10) described a case of P.E. in a 21 year-old girl, detected after an attempted suicide with carbon monoxide intoxication. When admitted to the hospital she was quite unconscious with a pulse rate of 48 per minute. She regained conscious 24 hours later and her heart and neurological status was then normal but the P.E. which persisted for another eight days, had completely disappeared 28 days after the intoxication.

As has been pointed out by several authors (11—20 26 27) difficulties may be experienced in diagnosing myocardial infarction in cases of P.E. In the present investigation, a case of this sort is described where myocardial infarction revealed, combined with both P.E. and atrioventricular conduction disturbance with Wenckebach's phenomenon. (Some aspects of this case were previously described by Ohnell (3).)

Previous investigations of P.E. with exercise tests

Feil & Brofman (25) have described three cases of P.E. investigated with exercise tests, according to Master's method, and one of them had "a history suggestive of coronary insufficiency" The exercise test was considered posi

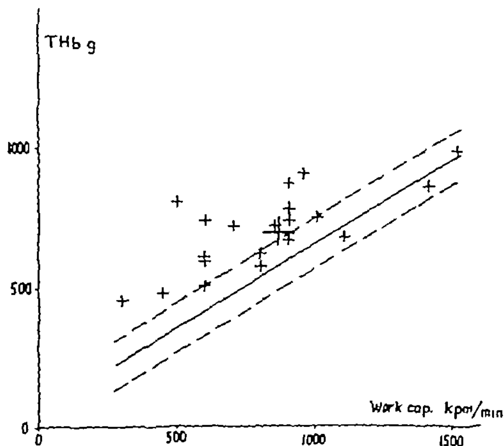


Fig. 43. Total amount of hemoglobin (ordinate) in relation to physical working capacity (abscissa). For further explanation see Fig. 44. The normal regression line equation, $y = 0.54\,x + 160$, $S_y = 88$, $= 0.93$.

P.E. type 1		P.E. type 2		P.E. type 3	
Case no.	Age in years	Case no	Age in years	Case no	Age in years
10	56	5	53	1	25
12	51	6	40	3	37
		7	[illegible]4	4	31
		8	26	9	24
		18	44	11	40
		19	43	13	18
		30	23	14	41
		35	43	15	21
				17	16
				20	59
				21	26
				22	1
				26	19
				29	56
				31	19
				32	23
				33	19
				34	29
Number of cases	[illegible]		8		18
Average age			37,3		29,1

Table 21 Age distribution of the material in the different P. E. types.

from the THb values, and is just below the normal variation. The values of only eight of the nineteen cases are within the normal variation all the others are lower The lowest PWC, when compared with the values obtained from the THb is that of case 14 a 41 year-old warrant officer with nervous symptoms but no signs of organic heart disease.

When compared with the values obtained from the heart volume (HV) the PWC is also lower than expected as is shown in fig 46 The average value is lower than the normal variation and of the nineteen cases investigated eleven showed lower values than the normal variation. The lowest values are those of case 3 a 37 year-old housewife, and of cases 14 and 26 both newly described.

The separation of P E cases in exercise tests from those with ischemic heart disease or myocardial changes of different etiology

It is a well known fact, which has been pointed out by several authors (11—20, 26 27) that it may prove difficult to establish the diagnosis myocardial infarction in a case of P.E. There is also a possibility of misinterpreting S—T T changes which appear in connection with P E during exercise tests as is demonstrated by case 10. The patient suffered from diffuse precordial symptoms, and in order to determine whether or not there was a coronary disease behind these symptoms, an exercise test was performed in another hospital, which was later repeated in our hospital with the same results. The Ecg series is shown in Fig. 40.

At the first examination the patient was suspected of having a coronary disease, because the delta wave, which appeared in connection with the pronounced S—T T changes during exercise, was not identified. The fact that the S—T T depression did not occur gradually but appeared during the exercise test, and then disappeared immediately after the exercise, did not indicate coronary disease, where the usual reaction is that the S—T T changes often continue during the first few minutes after the work has stopped.

In another case, a myocardial injury following a tonsillary infection, seems to have been explained in this way During his military service, the patient case 7 was treated for a severe tonsillitis with hemolytic streptococci and was suspected of having acute myocarditis in connection with this infection. In interpreting the Ecgs recorded at this time, the P.E. was not detected. When some years later the patient was reexamined on account of insurance, the Ecg at rest showed typical signs of P E. An exercise test was performed which showed a P.E. that disappeared during work. However there is an inversion of the Twave in lead CH during work and also similar changes in lead II immediately after work when the P E. has not yet returned. These T inversions are pathological and indicate a myocardial injury

The relationship between the extent of the S T T changes in exercise tests and clinical or other signs of organic heart disease, particularly cardiosclerosis

The cases have been divided into three age-groups. The first consisted of patients under 30, where the occurence of ischemic heart changes may be very improbable. The second was an intermediary group designed to indicate the two limits and the third consisted of patients aged 50 or over where a higher percentage of ischemic heart diseases was likely to be found than in the other groups. The results must be regarded with some reservation, however on account of the small number of cases in the last group.

Age-group		Number
1	16—29 years	14
2	30—49 „	10
3	50—59 „	5

Table 22

Distribution of the material by age groups.

Of the five cases in group 3 four have had either myocardial infarction or precordial pains of an angina pectoris character If we study the Ecg reactions of these five cases with regard to the S—T and T intervals, we shall find that in each of them there were changes which could have been interpreted as typical signs of coronary disease, if the P.E. had not been present. In the most accentuated cases, Nos. 10 and 12 the S—T T changes were registered during the exercise tests in all leads used as is shown in figures 40 and 41

great importance to be able to show the connection between P.E. and paroxysmal tachycardia, as an explanation of the latter symptom.

No earlier description of the physical working capacity in cases of P.E. seems to have been published It is interesting to note that the average value of PWC is lower than expected from both the THb and the HV and that in the former comparison, only eight of the nineteen cases investigated were within the normal variation, (± standard deviation) This is contrary to the opinion previously held, that P.E. is a quite harmless state.

It should be clearly pointed out that the material dealt with in this investigation was not primarily pathological. Some of the patients investigated here were, from the outset, suspected of having heart diseases and pulmonary diseases whereas others had symptoms and signs from quite different systems of organs, which do not affect the heart and circulation and there were also patients entirely free from any symptoms, where Ecg recordings were made only as routine procedure or for health certificates.

There were no evident signs of infectious diseases constituting etiologic factors in regard to P.E. in this material. Moreover with the exception of paroxysmal tachycardia, there were only seven cases in which heart symptoms to any considerable degree were found.

Changes in the S—T and T intervals are frequently observed during the tests, and plateau-shaped S—T depressions are often found, which are of the type considered typical of coronary heart diseases. A comparison made between a group of young patients and an older group where a higher per cent of coronary diseases may be expected, clearly showed that the S—T and T depressions observed in this material seem to be a function of the altered conduction conditions, and cannot be regarded as a sign of coronary disease. From this, it also follows that it may be impossible to get the normal Ecg signs of coronary disease in a case where P E. is present, which of course may make exact diagnosis more difficult in such cases.

Conclusion

An account was given of a study of twenty eight cases of preexcitation (P E.) investigated with exercise test and of the determination of the total amount of hemoglobine (THb) and the heart volume (HV) by the method described by Sjöstrand et al The relations of the factors to a normal material was also described The most common reaction during Ecg exercise tests is unchanged conduction conditions less common is the disappearance of the P E. and the development of P E. during exercise is regarded as a rare finding this may be of great diagnostic importance. The studies of the physical working capacity (PWC) showed that

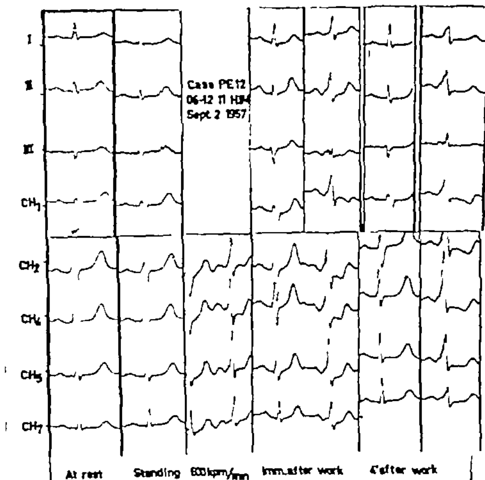


Fig 4

This patient was a 59 year-old man who had had typical myocardial infarction with Ecg changes indicating a posterolateral infarction and during the course of the disease a Wenckebach's phenomenon was manifested.

On the other hand, the Ecg series of a 16-year-old boy (case 17) is shown for comparison.

It appears evident that it is very difficult to draw any conclusions, with regard to the existence of coronary disease from the character of the S—T and T changes in a case of P.E.

CHAPTER VII

STUDIES ON ATRIOVENTRICULAR CONDUCTION DISTURBANCES DURING EXERCISE TESTS

Introduction

Atrioventricular block is defined as a disturbance of the conduction between the normal sinus impulse and the ventricular response. It is divided into different groups, usually two main groups:

A. Incomplete.
 1. First degree.
 2. Second degree.
  a. Periodic A V block.
  b. Constant A V block.
  c. Wenckebach's A V block.

B. Complete (third degree).

The first degree block may occur also without signs of organic heart disease, but several infectious diseases, as well as digitalis and quinidine, are regarded as its cause (17).

A—V blocks of the second and the third degree, however, are usually considered to result from organic injury. In this connection, the most common causes are assumed to be certain infectious diseases, coronary diseases and congenital changes such as ventricular septal defects, but in several cases the cause is unknown. Sometimes the state has a varying character depending upon the position of the body, pulse rate, vagal tone and other factors.

Earlier investigations into the reaction of incomplete A—V blocks during exercise

According to several authors (1—12) the P—R interval is, immediately after exercise, almost invariably either decreased to a greater extent than would correspond to the elevation of the heart rate or is quite independent of the latter.

Increase of P—R as compared with the value at rest, accompanied by an elevation of the heart rate, has been observed only in pathological cases (13). Several minutes after exercise the heart rate falls and P—R may become longer than at rest, especially in untrained or vasolabile persons (9, 14). This increase does not, however, exceed 0.02 seconds or the absolute value of 0.22 seconds.

Scherf and Boyd (1946) (18) reported that exercise may lead to a higher degree of block in the presence of partial A—V block.

However, Bengtsson (1956) (15) thorough study of these relations, where Ecg recordings were made not only after but also during exercise, showed that in healthy persons, both children and adults, there is an evident relation between the P—Q interval and the

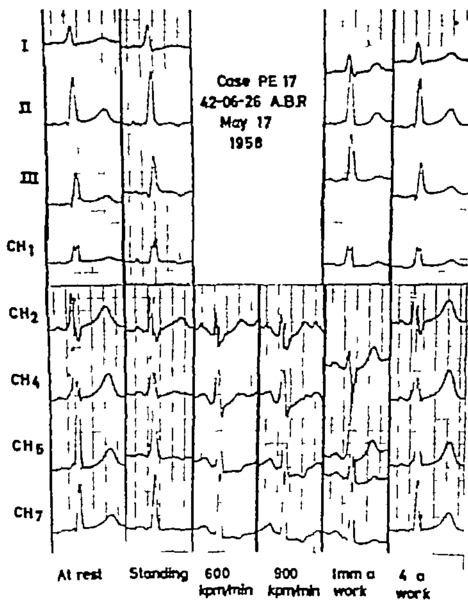

I
II
III
CH1
CH2
CH4
CH6
CH7
Case PE 17
42-06-26 A.B.R
May 17
1958
At rest
Standing
600
kpm/min
900
kpm/min
Imm a
work
4 a
work

Fig 43

Material and methods

The material was divided into two groups, incomplete and complete atrioventricular blocks.

The first group comprised six cases, all men, between 20 and 49 with an average age of 32 years.

The second group contained eight cases, between 15 and 50, with an average of 28 1 years. Six of them were men and two women

Further data are given in tables 26 and 27

As the P—Q time may often be difficult to measure at high pulse rates the values were obtained from more than one complex and if they differed, the average value of at least three beats has been given

Results

Incomplete atrioventricular blocks

Table 27 and fig 47 show that, with increasing pulse rate following physical work the P—Q time is shortened whereas, after work, the tendency is, as could be expected, to return to the P—Q time at rest. It is sometimes very difficult, however to measure the length of the P—Q intervals at high pulse rates accordingly in this material only two cases have been analyzed more thoroughly

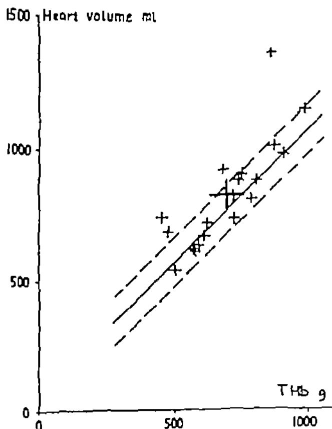


Fig 44. H rt volume (ordinate) in relation to total amount f hemoglobin (abscissa). Straight line represents the normal regression line obtained from d terminations in 58 healthy men, women and hildren (f Holmgren et al., 957 (8) with equation y = .0 x + 64, Sy = 93 = 93. Dotted lines indicate variation ± one standard error f estimate (Sy).

cious myocarditis with a prolonged P—Q time of about 0.26 seconds. Subsequently repeated Ecgs showed a normal P—Q time of about 0 16 seconds. There was an obvious increase in his antistreptolysine activity 720 units per ml but his blood sedimentation rate was normal.

Consequently this appears to be a case where the clinical findings suggest myocarditis involving the atrioventricular conduction system. Thus, the exercise test revealed a latent atrioventricular block in a case that had previous been regarded as cardiac neurosis.

Case 14 a 20-year-old conscript, had no case history of diseases involving the heart but his physical condition had always been inferior to that of his friends of the same age. Two comprehensive investigations in the same year 1957 revealed merely bradycardia, whereas the exercise tests showed disturbances in the atrioventricular conduction system after work During the first test, the P—Q time altered from 0.15 seconds immediately after work, to 0 36 seconds four minutes after work during the third test, the corresponding values were 0.14 and 0 35 seconds respectively The pulse rates in the different tests were rather similar when the alterations took place.

In the second test, Wenckebach s phenomenon was observed immediately after work and in several Ecg recordings made during the first sixty minutes after work, a variation between atrioventricular block of the first degree and Wenckebach s phenomenon occurred. When in an upright position sixty minutes after work, the P—Q time was quite normalized.

It should be pointed out that in the first test, when measuring the P—Q time at a pulse rate of 168 beats per minute a rather normal decrease to 0 12 seconds was observed this would not have revealed the conduction disturbance. In the last case the cause of the block was quite obscure.

Complete atrioventricular blocks

Since cases 1 4 and 6 had already been thoroughly studied by Holmgren et al. (27) they are only briefly described here.

In the eight cases studied here, the etiology of the A—V block appears to be of an infectious nature in cases 5 and 16 whereas a congenital disturbance is suggested in cases 1 4 6 and 7 In cases 8 the cause seems obscure, and in case 9 no information was available on this point. In case 8 there was in addition a left side bundle-branch block.

The behaviour of the eight cases during the exercise test is demonstrated in figures 48 49 and Table 26

1500 Heart volume ml.

1000

500

0

0 500 1000 1500

Work cap. kpm/min

Fig. 46. Heart volume (ordinate) in relation to physical working capacity (abscissa). For further explanation see Fig. 44. The normal regression line equation $y = 0.59 x + 90$ $S_y = 93 = 93$.

From figure 44 it is obvious that the cases in question have either a normal or a larger HV when compared with the values obtained from the THb. The average value is within the normal variation. No value is below the normal variation and the value, which shows the greatest deviation is that of a 19-year-old racing cyclist.

Physical working capacity in cases with P. E.

Fig. 45 shows that the values for physical working capacity (PWC), as defined by Sjöstrand et al., are either normal or lower when compared with those obtained from the THb. The average value is lower than expected

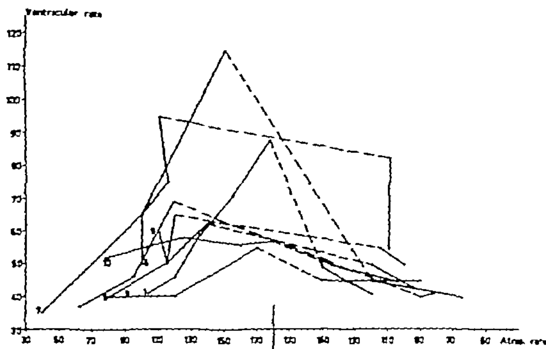


Fig. 49. Relation between ventricular rate beats per minute (ordinate), and atrial rate beats per minute (abscissa), during and after exercise test. The numerals represent the different cases.

Conclusion

Six cases are described where incomplete A—V block was observed at rest or developed during or after exercise. The two cases that are of the greatest interest had got either no diagnosis or previously the diagnosis cardiac neurosis. Before the test both had a normal P—Q time at rest; when the pulse rate increased following exercise, they showed a rather normal decrease in the P—Q time. Immediately after work, Wenckebach's phenomenon was observed, which suggested a latent injury of the A—V conduction system.

Exercise tests were used in the study of eight cases of complete A—V block. The relation between the atrial and the ventricular rate during and after the exercise tests is demonstrated graphically

The etiology of P. E.

In order to clarify the etiology of the P.E. on the basis of the experience gained from this investigation the following facts may be pointed out.

Case 13 had a toxic goitre with a basal metabolic rate of + 60 per cent and typical signs of thyrotoxicosis. Both before and during the exercise test, a P.E. was evident before treatment after thyroidectomy the test showed a quite normal Ecg both at rest and during work. A new Ecg at rest, made some time after the surgical treatment, showed a single P.E. complex, while the other Ecgs were quite normal. Consequently this case is fully in keeping with those described earlier. It is also of great interest to note that even the exercise reaction was normalized after surgical treatment.

The second patient, case 16 had a series of Ecgs at rest with P.E. He suffered from vertigo and some trouble in the region of the heart probably connecting with his exposure to toxic gases at his work place. Unfortunately it was impossible to get him to undergo an exercise test before he changed his work place and was free from symptoms. The Ecg at rest then showed normal tracings as well as the reaction during work.

Discussion

Judging by the literature on P.E., it appears to be the generally accepted opinion that in most cases, this is quite a harmless state without any pathological significance. Thus, Lepeschkin (1951) (6) reports objectively normal hearts in 60—70 per cent of cases with P.E. There are also numerous factors, however which influence the state, for instance, hyperthyroidism which was found in one of the cases in this material. In this case, the P.E. disappeared after adequate treatment of the toxic state.

Earlier investigations, in which exercise tests were used, are very rare it does not appear that methods were applied consequently which made it possible to study the shape of the QRS complexes also during the exercise.

From this material it is evident that the most common reaction of the P.E. — Ecg at rest is, that the P.E. persists during and after an increase in the pulse rate following exercise. This seems to be also the result even if the test is repeated after some time. The second reaction type, that the P.E. disappears during exercise is not so common in this material the third type, P.E. appearing during work in cases with normal intraventricular conduction at rest, seems to be a relatively rare finding.

It is quite evident, that a method where Ecg recordings can not be made during exercise, as well as after exercise is inadequate for the detection of such phenomena. It is perhaps open to discussion whether this reaction type is of any interest from a clinical point of view. Here, however it seems to be of

CHAPTER VIII

ATRIAL FIBRILLATION AND FLUTTER DEVELOPING DURING EXERCISE TESTS

Introduction and literature review

Atrial fibrillation is a rather common complication of heart diesease, particularly when this is of a valvular or cardiosclerotic nature. Sometimes it appears also in persons presumed to be healthy where no organic heart disease has been observed or will be subsequently found.

Different causes of such states are described, for instance thyrotoxicosis and alcoholic excess (Evans 1960) (2).

Several authors, for instance Goldhammer and Scherf (1932) (3) and Jervell (1941) (5) have stated that exercise is a cause of atrial fibrillation in healthy persons.

Scherf and Schaffer (1952) (8) Hay and Jones (1927) (4) and Rumbal and Acheson (1960) (7) have described atrial fibrillation following long distance walking and ski races, usually in competitors who finished in an exhausted condition. In the report last mentioned, 660 RAF officers, who had no heart symptoms were examined with Ecg before, and at different times after strenuous work, consisting of running down and up a flight of stairs. One case of transient atrial fibrillation was found.

In a study of 125 healthy children and adults, where, in principle, the same method was employed as is used here Bengtsson (1957) (1) did not found a single case of atrial fibrillation or flutter during or after exercise.

Material

The material in this investigation consisted of four cases.

The age limits were 26 and 48 years, with an average age of 39 years.

All the cases were men who, for different reasons, had been admitted to the hospital for exercise tests. Further data are given in table 28

in this material the P E. cases had, in general a lower PWC than was expected with regard to the values obtained from both the THb and the HV This is in contrast to the rather widespread opinion that P E. is a quite harmless state which does not involve the heart and circulatory system.

References

1 *Wolff L., Parkinson J & White P D.* Am. H art J. 5 685 930.
2. *Ohn II, R. F* Acta Med. Scand. suppl. CLII 944.
3. *Ohnell R. F* Nord. Med. 38 7 1948
4. *Wolferth C. C & Wood F C.* Am. Heart J 1450 94
5 *Prinzmetal, M Corday E., Brill, I C., Oblath R. W & Kruger H E* The uricula arrhythmias, vol. I Chs les C. Thomas, Publisher Springfield, Ill U.S A. 1952.
6. *Lepeschkin E.* Modern electrocardiography Vol. I The P-Q-R S-T U Complex, The Williams and W lkins Company Baltimore 95
7 *Jerv II, O* Nord. Med. 47 94
8 *Wolff L., White P D* Arch I Med 8 1446 1949.
9. *Strong, J A* Lancet 256 959 949.
0. *Dommer E., Merlen, J F* Acta Cardiolog 3 946.
Wolff L Richman J L Am. Heart J 45 545 1943
2. *Eckert H* Ann. Int. Med. 907 944
3. *Goldbloom, A. A., Dumonus, A. A* Ann I Med. 5 36 946.
4. *Rin ler S H T avell, J* Am J Med. 3 06 947
15 *Tamagua I G Batterworth J S Poin d xter C. A.* Am. Heart J 35 948 1948
16. *Kutin A. D Robb G P* Am. Heart J 37:249 949.
7 *Levene H D Burge J C.* Am. Heart J 36:431 948
8 *Stern I Wroblewski, F* Am. Heart J 41:614 95
9. *Goldberg, H H Lewis S M* Am. Heart J 40 614 950.
20. *Zoll P M Sacks, D R.* Am. Heart J 30 5 7 945
Lamb A E. Med. Times and Long Island Med. J 6 54 933.
22. *Master A. M et al.* J Mount Sinai Hosp 4 00 937
3. *Mikdlhouses, T K dts, Z* Z. Klin. Forsch. 35 388 943.
24. *Willis, F A., Carryer H M* Proc. Mayo Clin. 438 946.
5 *Feil, H Brofman B L.* Am Heart J 45:665 953
6 *Graybiel J* New England J of Med. 59 369 958
7 *Karvo I* Am. Heart J 55:406 958
8. *Holmgren A., Jonsson B Levander M Linderholm, H Sjostrand T and Strom, G* Acta Med. Scand., 53:4 3 957

short observation time and a number of nervous symptoms, it has proved impossible to get the patient who is a refugee to undergo another exercise test.

In case 3 (Fig. 50) atrial fibrillation was found at rest, in an otherwise healthy 26-year-old quartermaster-sergeant. Two previous Ecgs at rest showed atrial fibrillation and VES. The patient had at rest, before the exercise test, a regular sinus rhythm but atrial fibrillation developed under the second load. The sinus rhythm returned after work and an Ecg obtained 6 minutes after the work had been stopped, showed also coupled VES in bigeminal and trigeminal rhythm. In addition to the data given in table 28 it may be mentioned that the values of the antistreptolysine activity were near the upper limit, 320 and 440 units per ml. No other signs of infections in progress were found.

Case 4 a 50-year-old railway official, without any previous diseases of interest, had had attacks, since about thirteen years, of palpitation with a very high frequency particularly after physical and mental strain The general investigation showed no signs of organic heart disease. Blood pressure and roentgenological heart volume were normal in the upright position. The first exercise tests in 1957 showed sinus rhythm and pronounced S—T T-changes during all the tests the latter were difficult to evaluate, however because the patient had been treated with digitalis. In a second test made three months later an atrial flutter with 2 1—3 1 blocking was observed under the third load. The flutter still remained 2½ hours after the work had been stopped. The third test showed no arrhythmia, but this time the test was stopped at a relatively low pulse rate. The fourth test showed about the same pattern as the third did. When the third test was made the patient was digitalized but 33 days before the fourth test the digitalis treatment was interrupted. This is too short a period to exclude a digitalis effect on the S—T and T intervals (Nordström—Öhrberg 1959) (6) Therefore the Ecg could not be evaluated in this respect.

Discussion

Lewis's theory of the genesis of atrial fibrillation and flutter which previously won general acceptance has been called in question during the last decade as a result of the studies on atrial arrhythmias by Prinzmetal et al. The view that is most generally held at present, appears to be a compromise between the "focal theory" advanced by Prinzmetal et al. and Lewis's "circular" theory by means of the compromise the two mechanisms do not exclude each other

The cause of atrial fibrillation or flutter in cases of atrial dilatation is rather generally regarded as being the sequel of the stretching effect on the muscle fibers. This may also be the explanation of the cases where the changes appear in presumably healthy men, during heavy exercise. But also other factors, such as localized myocardial

heart rate during work. Bengtsson stated that in all age-groups irrespective of the initial value at rest and of sex the P—Q interval decreased during work done at a heart rate of about 170 beats per minute to the same value, 0.11 seconds.

If the prolonged P—R interval at rest is due to pathological involvement of the A—V node P—R usually shows either no change or a further increase after exercise: less commonly it decreases, but, in this case, normal values are seldom obtained and a secondary increase of the P—R beyond the prolonged value at rest usually occurs several minutes after exercise (16).

Consequently it seems to be of the greatest interest that the P—Q interval reaches this level of 0.11 seconds at a pulse rate of about 170 per minute or that it has at least a tendency to decrease to approximately this value and then to increase again after the work has been stopped. It is often difficult, however to get exact values for the P—Q time at higher pulse rates and sometimes no distinct P—Q interval can be delimited at all.

Complete atrioventricular block and exercise

Circulatory problems at rest and during muscular work, in cases of complete heart block have previously been studied by inter alia Menne and Lauter (19) Karn and Werkö (20) Liljestrand and Zander (21), Hyman (22) Ellis and Weiss (23) Lagerlöf and Werkö (24) Kelly and Bayliss (25) and Pa l, Rudolf Ongley and Nadas (26).

In 1959 Holmgren Karlberg and Pernow (27) studied circulatory adaption at rest and during muscular work in patients with complete heart block. Right heart catheterization was performed in two of the four cases described. The latter are included also in the present material. One of these cases, where ventricular premature beats developed during work, is of special interest. This was supposed to be the reason why the patient had such a good physical working capacity that he could play football and do physical training three times a week. The investigation showed, however that the premature beats had not sufficient effect to prevent the blood pressure to drop during the long periods between the ordinary ventricular contractions.

In their previous studies of complete block, Erlanger and Blackman (28) Hecht (29) and Carlsten (30) found that there is a tendency to shorten these periods between two auricular contractions, during which a ventricular contraction occurs. Carlsten (30) also stated in a study on the effect of standing position on seven cases of complete heart block that, in a recumbent position, six of them had a sinus arrhythmia and that the atrial rhythm became regular in each case.

Carlsten and Rudhe (31) found, in an electrokymographic study of total heart block, that there seems to be a relation between the atrial arrhythmia and the filling and emptying of the atria.

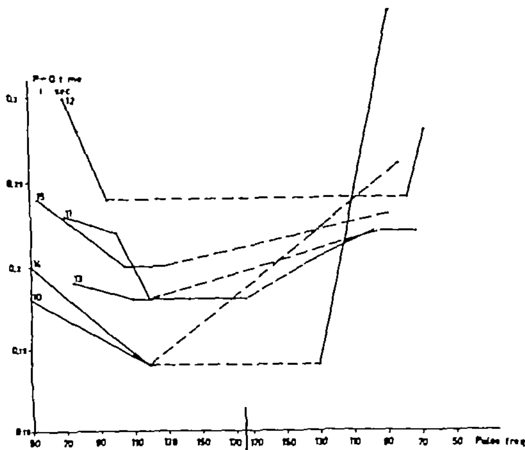


Fig. 47. P—Q time in second (ordinate) in relation to pulse rate beats per minute (abscissa) during and after exercise. The numerals represent the different cases.

In case 13 (a 37 year-old worker) the P—Q time is only shortened from 0.19 seconds at a pulse rate of 75 beats per minute at rest, to 0.18 seconds at a pulse rate of 176 which according to Bengtsson, should be an abnormal reaction.

Cases 10 and 14 show a normal P—Q time at rest but both reveal conduction disturbances after exercise. In case 10 (a 23 year-old teacher) Wenckebach's phenomenon appeared in the first test, immediately after work, at a pulse rate of about 120 beats per minute in the second test it appeared at 110 beats per minute. The interval between the two tests was about 6 weeks. This patient has suffered from scarlet fever twice in the same year 1950 and the symptoms previously mentioned, first appeared after this period. An Ecg at rest then showed one isolated sino-atrial blocked beat but was otherwise normal. In 1954 he was hospitalized because of a suspi

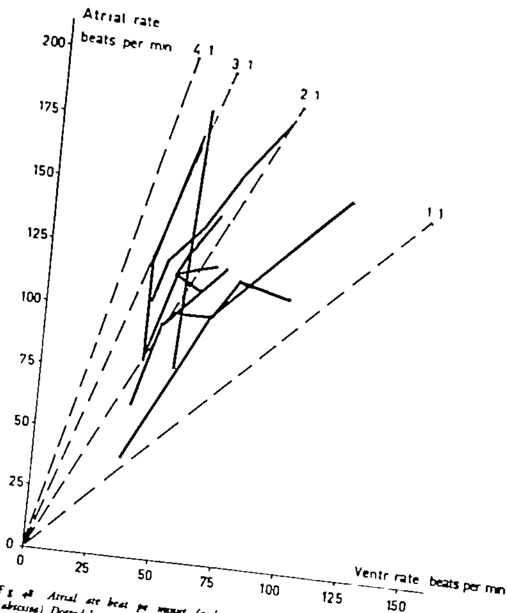


Fig 48 Atrial ate beat per minut (ordinate), in relation to ventricular ate beats per min abscissa) Dotted lines represen various fixed relation between the atrial and ventricular ates.

References

1 *Kihl, J. Herrmann, A. and Spiegl, E.* Ztsch f Kreisla fforsch. 27·659 935
2. *La cattin P and Schuler A* Klin. W bnsch 17·6 5 1938
3 *Reindell, H* Dtsch. Ar h. f Klin. Med. 8 ·483 1938 18 ·506 1938
4. *Knott Di* (Münster) 938
5 *Laurentius, P* Ar h. f Kreisla fforsch 6 83 1940
6. *Herz m, A.* Ztsch f kreisla fforsch 3 6 1 940
7 *Barrow W H and Oue R A* A h. I t. Med 7 ·1547: 943
8 *Schlomka, G* Arbei sphysiol 8·725 935
9 *Schlomk G and Reindell H* Ztsch f Klin. M d 3 3 3 936
0. *Mose D* Coore circolar 6·65 942. *Sa slabis M* Acta Med. Scand. 8 5 946.
von der Weth G Verh Dtsch. Ges. f Kreislaufforsch. 194 939
1 *Lepeschkin, E* Modern Electrocardiog aphy Vol The Williams and Wilki Co Baltimore 95
4 *Delius L. and Reindell, H* Dtsch Arch. f Klin. Med. 8 ·167 937
5 *Bengtsson E* Acta Med. Scand. 5412 5 956
6 *Arenle F* Das Belastungselektrokardiogramm und das Steh-EKG. Georg Thieme Leipzig 946
7 *Goldman, M J* Pri ciples f Clinical Ele trocardio raphy Lange Medical Pub-l ions, Los Altos, California, 956
8 *S herf D. and B yd L. J.* Clinical Ele trocardio raphy Philadelphia 946, J B Lippincott Co
9. *Menne T and Laster S* Ztschr Klin. Med. 1 9 96 93
0. *Karne, H and W rkö L.* Nord. Med. 48 930 952
Liljestrand G and Zander E Acta Med Scand. 66 50 927
Hyman J A. M A 94·27 927
3 *Ellis, L B and Weiss, S* Am. J Med S. 82 94 93
4 *Lagerlöf H and Werko, L* Cardiol. 13 4 948
5 *K lly H G and Bayliss R J S* Lan et 07 949
6 *Paul M H Rudolph, M A Ongley P A and Nadas, A. S* Ci culation 4198 956
7 *Holmgren A Karlberg P and Pernow B* Acta Med. Scand. 64 9 959
8 *E linger J and Blackman J R.* Heart 77 909 9 0
9 *Hecht A F* Erg. d in Med. Kinderh 324 9 3
1 *Carlsten A* Acta Med. Scand. 49.2 954
1 *Ca lsten A and Rudhe U* Acta Radiolog 4 3 6 954

Results

As is evident from table 28 only on of the patients had a history of severe or recurrent infectious diseases, and none had had heart symptoms of an anginal type.

Unfortunately it has not been possible to study the relations between blood volume heart volume and working capacity as described by Sjöstrand et al., because the exercise tests were stopped at such an early stage that the values could not be estimated

In an upright position, blood pressure and heart volume were normal in all ases ex ept one where an increased heart volume was found.

Case 1 was later treated in the hospital for decompensation of the heart, with atrial fibrillation which was cured with digitalis and quinidine From a clinical point of view the case as considered to be a myocardial injury following a chronic urinary infection, resulting in pelvospondylitis ossificans (Bechterew).

In case 2 it seems very likely that the atrial fibrillation was induced by thyro d extracts, but, on account of the

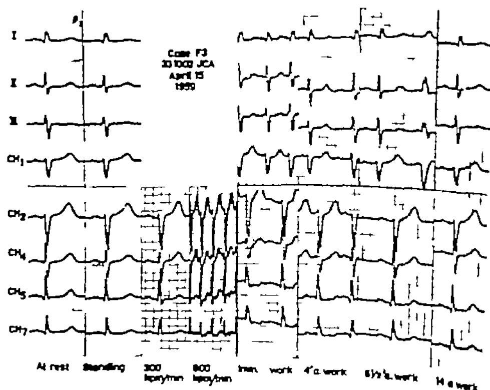


Fig 5

injuries of infectious or ischemic origin or a toxic action may be responsible for these changes.

The study previously referred to, by Rumbal and Acheson (1960) (7) of 66 healthy RAF officers is of rather little significance in elucidating the frequency of arrhythmias that develope during "strenuous work" because no Ecg recordings were made during the performance of the exercise. The frequency of arrhythmias might have been higher if Ecg recordings had been made also during the exercise and, in the material consisting of four patients in this investigation the atrial fibrillation in case 2 might have been missed, if an Ecg recording had not been made during the exercise.

"Strenuous work" is, moreover a very relative conception in their method, e.g., depending upon such factors as the weight of the subjects, the height of the stairs and the speed.

The restricted number of cases in the present investigation does not justify the drawing of any definite conclusions about the arrhythmias but it seems probable that infectious or toxic factors may have played a rôle in the first three cases, even if the evidence for this assumption seems rather vague. Myocarditis must be regarded however as often very difficult to diagnose. The history of the fourth case did not support any organic cause.

Conclusion

Four cases, where atrial fibrillation or flutter developed during exercise tests, have been analyzed. Three of the four cases appear to have a toxic or myocarditic etiology.

References

Bengtsson, E. Acta Med. Scand. 154: 5, 1956.

Evans, W. Progr. in Cardiovasc. Diseases 480 962.

3. Goldhammer, S. and Scherf, D. Ztsch. f. Klin. Med. 54 932.

4. Hay, J. and Jones, H. W. Brit. Med. J. 359 9 7

5. Jervell, O. Acta Med. Scand. 3 64 94

6. Nordström-Öhrberg, G. Personal communication.

7. Rumbal, C. A. and Acheson, E. D. Brit. Heart J. 14 5 96–

8. Scherf, D. and Schaffer, A. I. Am. Heart J. 43:9 7 952.

TABLES

Nos 23, 24, 25, 26,
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Pulse rate (beats per min) [wh]en disappearing	R—R time (seconds) when disappearing	Infectious diseases of interest	Subjective symptoms	Diseases or symptoms of interest
— 160—100 120— 92 175—107	 0.38—0.60 0.50—0.66 0.35—0.55	+	+	
150—106 110— 78	0.52—0.74 0.55—0.75	+	+	Poliomyelitis Angina pectoris
180—117 125	0.51—0.64 0.45	+	+	
82— 72	0.72—0.82	(+)	+	Cushings disease? Blood pressure175/110 Angina pectoris
163—127 168—150	0.37—0.47 0.40	—	(+)	
Returns at 600 kpm/min 127— 93	0.48—0.65	—	+	Angina pectoris Blood pressure 200/105
90— 85	0.68—0.72	+	+	Angina pectoris
150—115	0.45—0.60	—	—	
highest freq. 158 beats/min. 140— 85	0.42—0.46	—	(+)	Ventricular septal defect

branch block appearing during exercise test.

Translated by

George R. Otter B A.

[illegible] GÖTEBORG [illegible]
BOKTRYCKERI AKTIEBOLAG
[illegible]

Increased blood pres (>150/100) N = normal	THb (g)	Heart vol (estimated from the THb) (ml)	Heart vol. (ml)	PWC (estimated from the heart vol.) (kpm/min)	PWC (estimated from the THb) (kpm/min)	PWC (kpm/min)
N	—	—	—	—	—	—
N	455	525	740	950	550	300
N	740	800	880	1200	1075	900
N						
N	620	700	720	925	850	800
N	720	800	735	925	1050	700
N	5 0	650	620	750	775	900
N	785	850	810	1075	1150	900
170/100						
N	720	800	820	1100	1050	850
N	575	630	610	725	775	800
N	480	550	685	850	600	450
N	805	880	880	1200	1200	500
N	—					
N	868	925	1010	1400	1350	900
N	612	675	670	875	850	600
N	595	650	635	750	800	600
170/100						
N						
N	750	825	905	1225	1110	1000
N	860	925	1360	1980	1300	1400
N	680	750	920	1250	950	1100
N	505	580	540	600	650	600
N	983	1025	1150	1630	1550	1500
N	905	970	980	1350	1400	950
N	—	—	—	—	—	—
N	—	—	—	—	—	—
N	—	—	—	—	—	—

nation

The present thesis is based on the following papers:

I. Incidence of Peptic Ulcer in Diabetes Mellitus.
Acta Med. Scand. 164 463 1959

II. Gastric Secretion of Acid in Diabetes Mellitus during Basal Conditions and after Maximal Histamine Stimulation.
Acta Med. Scand. 170:59 1961

III Gastric Emptying in Diabetes Mellitus.
Acta Med. Scand. vol. 170 1961 in press

IV The Gastric Mucosa in Diabetes Mellitus. A functional and histopathological study (Together with L. Angervall and K. E. Lehmann)
Acta Med. Scand. 169:339 1961

V Effect of Intravenous Infusion of Glucose on Gastric Secretory Responses to Feeding in Pavlov and Heidenhain-pouch Dogs. (Together with A. Muren).
Acta Physiol. Scand. vol. 52, 1961 in press

In the following these publications are referred to under their Roman numerals. Some parts of Chapters II and IV have not been published before.

CHAPTER II

Gastric Secretion of Acid in Diabetes Mellitus

Gastric secretion of acid was studied in a material of diabetic patients (Paper II). In both men and women, basal secretion and secretion after maximal stimulation with histamine were lower in diabetics than in control subjects. Possible causes of the low secretion of HCl will be given more particular consideration in this chapter as follows.

1 Effect of hyperglycaemia on gastric secretion,

2 Influence of endocrine factors on gastric secretion,

3 Blood vessel changes and gastric secretion,

4 Influence of lesions in the autonomous nervous system on gastric secretion;

5 Influence of inflammatory changes in the gastric mucosa on gastric secretion,

6 Changes due to deficiency

1 Effect of hyperglycaemia on gastric secretion

A Effect of glucose by mouth on gastric secretion.

The literature contains a good deal of information on the inhibitory effect which glucose has on gastric secretion and gastric motility The majority of the accounts describe experiments with the direct introduction of various forms of sugar into the gastro-intestinal tract usually leading to diminished secretion of acid. The inhibiting effect of glucose on secretion in the stomach has been considered to be purely osmotic, as a corresponding effect has been obtained with hypertonic sucrose and sodium chloride Among others Horstmann (1946) investigated the effect of glucose administered perorally after stimulation either with Ewald's test meal or with a water test meal. He obtained low values of acidity if the sample was collected [illegible] hours after the introduction of the glucose

Reduction of acidity may be due to the following

Reduction in the quantity of gastric juice secreted,

Diminishing acidity

Slowing down of gastric emptying with a consequent dilution of the gastric juice.

By means of the serial test meal Hunt et al. (1951) were able to show that sucrose administered with test meals has an inhibiting effect on emptying as well as on secretion of the parietal component, pepsin and non parietal component. It is probable that this inhibition is elicited by chemoreceptors in the duodenum and small intestine

B. Effect of intravenous administration of glucose on gastric secretory responses to [illegible], feeding, and insulin stimulation in dogs

The stimulating effect of hypoglycaemia on the secretion of gastric juice is well known.

ACTA MEDICA SCANDINAVICA

SUPPLEMENTUM 368

GASTRIC FUNCTION IN DIABETES MELLITUS

A CLINICAL AND EXPERIMENTAL STUDY
WITH SPECIAL REFERENCE
TO GASTRIC SECRETION OF ACID

By

GERHARD DOTEVALL

ACCOMPANIES VOL. 170

GÖTEBORG 1961

against a centrally elicited inhibition on the cortical or subcortical plane, but there is hardly anything which directly supports this theory either Investigations by Day and Komarov (1939) however show that the gastric secretion elicited by sham feeding is rapidly inhibited by glucose, while secretion brought about by electrical stimulation of the vagus nerve in the throat does not elicit so strong an inhibition on administration of the same quantity of glucose.

As regards the peripheral effect of hyperglycaemia, previous investigators have argued that this is essentially an osmotic phenomenon. The present experiments do not support this assumption. The doses of glucose employed in our experiments however were as a rule lower than had been employed previously and the method differed from those of earlier investigations in that the glucose was infused over a longer period, usually 30 minutes. Corresponding amounts of saline solution of the same osmolarity as the glucose solution, administered over the same period of time produced no inhibition either of secretion elicited by n ulin r of secretion after feeding

C Eff t of intravenous infusion of gluc n gastric secretory re ponse t diff ... hemical drugs.

Recent tudies (Dotevall) nd M ren 1961) sho that the nhib t ry effect of hyperglycaemia on g tri secret on alu peripheral A pe l m nary ep rt n the re ult btai ed h

C the secret t r l d b mea s f an su ... ec er ... hu h d

mecholyl and urecholine and, in addition, by histamine

a. Carbachol.

In both Pavlov pouch and Heidenhain-pouch dogs an inhibition of carbachol stimulated secretion was obtained on intravenous administration of glucose, using the technique described earlier (Paper V) (Fig 1)

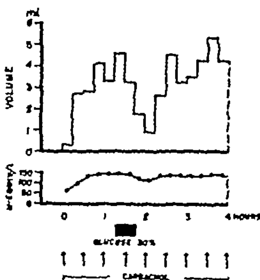


Fig 1
Effect of glucose infusion on the gastric secretory response to carbachol.

b. Mecholyl and urecholine

In the case of secretion elicited by mecholyl and urecholine also an inhibition was obtained in the majority of experiments by mean of intravenous infusion of glucose though the inhibition was not so pronounced or regular as with carbachol stimulation

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necessary to repeat gastric secretion studies in the same patient at different steady state levels of blood sugar to prove this point. It is possible that this inhibition is vagally conditioned and affects the gastric secretion directly and/or indirectly. Another possibility is that long-standing hyperglycaemia may in the same way as a vagotomy diminish the response after histamine stimulation, probably through a reduction in the number of parietal cells (Oberhelman and Dragstedt, 1948).

2. Influence of endocrine factors on gastric secretion

Clinical and experimental data indicate that there is a relationship between gastric function and endocrine activity. Thus the pituitary gland, the thyroid and suprarenal glands, as well as the endocrine apparatus of the pancreas may affect gastric secretion, at the same time as in diabetes mellitus these organs may to a greater or lesser extent participate in the disease.

A. Influence of the endocrine apparatus of the pancreas on gastric secretion

The indirect influence of insulin on the vagal phase of gastric secretion is relatively well known and has been discussed in another connexion. In other respects the connexion between gastric secretion and the endocrine apparatus of the pancreas is still obscure. Investigations by Zollinger and Ellison (1955) have shown, however, that certain tumours originating in the islet cells of the pancreas may stimulate gastric secretion, with a higher incidence of ulcer as a result.

During recent years an increasing number of cases of Zollinger-Ellison syndrome have been diagnosed. [illegible] tumour extract taken from a patient with the Zollinger-Ellison syndrome ([illegible] et al. (1960) have succeeded [illegible] substance with the same chem[illegible] ph[illegible]logical properties as the antral hormone gastrin. On the other hand the same extraction technique has so far not succeeded in isolating any substance similar to gastrin from normal pancreatic tissue taken from pig.

Glucagon, the formation of which is probably associated with the alpha cells in the pancreas and possibly with silver cells in the gastrointestinal tract, has an inhibiting effect on gastric secretion (see Paper II and IV). In experiments on animals, glucagon has a diabetes-inducing effect (Salter et al., 1957). The part played by glucagon in human beings under physiological and pathological conditions is still not clear, probably because of the imperfect methods we have for determining the presence of glucagon in the organism. Whether the secretion of gastric juice is influenced under physiological conditions also by hormones from the endocrine apparatus of the pancreas in the direction of stimulation as well as that of inhibition is still obscure.

B. Influence of pituitary gland, suprarenal glands and thyroid gland on gastric secretion

Animal experiments have made it fairly certain that most gastrointestinal glands do not preserve their structure and function in [illegible]ious disturbances of the endocrine sys-

CONTENTS

hypophysectomy is shown in Fig. 3. After complete hypophysectomy the secretion of HCl per hour decreased by an average of 50 in all the patients examined with cortisone substitution (25 mg a day). In 4 out of 5 patients where both cortisone and thyroid substitution were employed, or where, on account of incomplete hypophysectomy the patient showed no thyroid insufficiency and was therefore treated with cortisone only the secretion of HCl rose after the operation. Three of these patients had diabetes and one had carcinoma mammae with acromegalia.

One patient (Case No. 9) was examined three times before the operation, after the operation with cortisone treatment only and with indication of thyroid insufficiency and finally with both cortisone and thyroid substitution. After thyroid treatment, this patient showed a slight increase of HCl secretion compared with the post-operative secretion without thyroid hormones. The secretion was lower than before hypophysectomy however.

In order to investigate the error of the method after maximal stimulation with histamine, double determinations were made on 8 subjects at different secretions. At small volumes, the difference between two determinations, expressed in mEq/hr was very small. At larger volumes the difference was greater. In no case, however was the difference greater than 12 %. The differences before and after hypophysectomy as may be seen in Fig. 3 are of a completely different order.

b. Discussion

The material reported here is still too small to allow of any safe conclusions being drawn. As no data on the effect of hypophysectomy on gastric secretion in man have been found in the literature, a discussion of the results obtained seems to

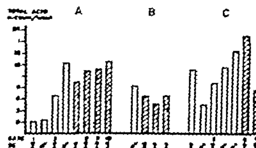


Fig. 3
Gastric secretion of acid before and after hypophysectomy. Maximal histamine stimulation.

Cases 1—6 diabetics.
Cases —10 patients with cancer mammae and metastases.

A. Gastric secretion of acid before hypophysectomy

B. Gastric secretion of acid after complete hypophysectomy. Patients treated with corticoid hormones only

C. Gastric secretion of acid after complete and incomplete hypophysectomy

Cases 3 and 9 — complete hypophysectomy patients treated with corticoid and thyroid hormones.

Cases 2 and 6 — incomplete hypophysectomy patients treated with corticoid and thyroid hormones.

Cases 1, 5 and 8 — incomplete hypophysectomy patients treated with corticoid hormones only. No clinical signs of insufficiency from the thyroid gland.

GENERAL INTRODUCTION

The clinical observation that peptic ulcer occurs more seldom in diabetics than among others directed my interest to study some aspects of gastric function in diabetes mellitus. As a consequence of the results obtained successively the following main problems were taken up for investigation.

To determine whether the supposed lower incidence of ulcer in diabetes mellitus is real or not (Chapter I).

To study the gastric secretion of acid in diabetes mellitus and to analyse the lower secretion of HCl from the following three aspects in particular: the influence of hyperglycaemia, the influence of endocrine factors, to examine whether diabetics have changes in the gastric mucosa also and if so to investigate the significance of these changes (Chapters II and V).

To study the emptying of the stomach in *diabetes mellitus*, and the reasons for changes in the rate of emptying in different forms of diabetes (Chapter III).

To explore the connection between diabetes mellitus, achlorhydria, atrophic gastritis, and latent and manifest pernicious anaemia (Chapter IV).

In the present work data obtained in the Papers I to V will be integrated and discussed in further detail. Since the various investigations overlap slightly and as new results are reported in this work, the chapter division does not coincide with the different papers referred to by Roman figures.

be justified, however. The part played by the pituitary in the regulation of the gastric secretion is still not clear. In spite of extensive research on experimental animals. After hypophysectomy, as previously mentioned, one gets a change of glandular structure and a reduction in gastric secretion, HCl as well as pepsin secretion. In animals, hormonal substitution after hypophysectomy does not give complete restitution of the structure and function of the gastric glands. A moderate effect has been obtained with cortisone, hydrocortisone, STH and thyroid hormones. This applies to the structure of the gastric chief cells in particular. But cortisone, and possibly thyroid hormones also has an effect on the parietal cells and on HCl secretion (for literature, see Baker 1957). From the investigations on experimental animals and the results of those on human beings published here, it seems likely that the pituitary gland in some degree regulates gastric secretion via subordinate endocrine organs, at any rate via the suprarenal cortex and the thyroid gland.

The observations made on 4 patients after complete hypophysectomy with cortisone substitution only tally well with the information previously obtained from animals. On the other hand, with diabetes patients who after hypophysectomy were given cortisone, and thyroid substitution treatment if signs of thyroid insufficiency were present, the results obtained diverged in a marked fashion from previous results in that a *significant rise in the secretion of HCl* took place after maximal stimulation with histamine. At the present time it is difficult to evaluate the results. The investigations, however, give some support for the assumption that the low HCl secretion in diabetes mellitus may in part be due to endocrine factors. The possibility that in these cases the pituitary gland may have a direct or indirect inhibitory effect on the secretion of gastric juice must be taken into consideration.

3 Blood vessel changes and gastric secretion

During recent years more and more interest has been directed to the study of blood vessel changes in diabetes mellitus. Most attention has been devoted to blood vessel changes in late complications of diabetes, while few investigations have dealt with the vascular changes that may occur in earlier stages of the disease.

4.1 *Vascular changes in diabetes mellitus*

Bárány (1955) examined 120 male diabetics between 15 and 30 years of age without indication of vascular occlusion. He found a reduction of heat dissipation during body warming, as well as of the intracutaneous radioactive sodium clearance. He came to the conclusion that the primary cause of the pathological heat dissipation in diabetics was a capillary damage which, in its turn, through a diminished inactivation of catechol amines, gave a secondary vaso-constriction of the vessels of the skin. Sigroth (1957) studied skin temperature in diabetics during indirect warming and during post ischemic hyperaemia. Reduced vascular responses were found, and improvements of

CHAPTER I

Peptic Ulcer and Diabetes Mellitus

The connexion between peptic ulcer and diabetes mellitus has been discussed by a number of writers (for literature, see Paper I). In most of the published reports the incidence of ulcer appears to be lower among diabetics than among the rest of the population. In these reports, however no regard has been taken of sex, age-distribution, and duration of the diabetes.

In Paper I, the incidence of gastric and duodenal ulcer has been studied in a diabetic material consisting of 1,[illegible]18 diabetics. Only patients with radiologically demonstrable niche were included in this material. 22 diabetics proved to have ulcer, 9 of them duodenal and 13 gastric ulcer. The incidence in this material was compared with the incidence in a larger normal material (Tomenius, 1955), account being taken of the above mentioned factors of sex, age-distribution, and duration of diabetes. A statistical computation for a control material of the same composition as the own gave an expected incidence of ulcer of 46 cases: 33 cases of duodenal ulcer, and 13 of gastric ulcer. Thus the under-representation of ulcer in diabetes mellitus for the actual material referred only to patients with duodenal ulcer. The proportion of duodenal to gastric ulcer in different surveys (for literature, see Tomenius, 1955) varies between 1.3 and 7.7. The corresponding ratio in the present diabetes material was 0.7.

Since the investigation reported in Paper I was published, Segovia et al. (1960) have studied the connexion between diabetes mellitus and gastro-duodenal ulcer. Their results confirm the low incidence of ulcer in diabetes mellitus. They had only 28 peptic ulcer cases among 3,990 patients with diabetes mellitus.

After a duration of diabetes of over 15 years the incidence of ulcer appears to increase again, approaching normal values. This may be associated with progressive diabetic angiopathy in the digestive tract also. Even small quantities of HCl may be sufficient to produce peptic ulcers in the stomach as well as in the duodenum. The reason for the lower incidence of duodenal ulcer is discussed in Paper I. As one of the most important causes of duodenal ulcer is hypersecretion of HCl, the result of this investigation led to a study of HCl secretion in diabetes mellitus, the result of which is reported in Chapter II.

with clinical signs of diabetic late complic ations also would further reduce the func tioning of the gastric mucosa, and would explain the lower secretion of HCl in patients with clinical signs of late com plications (Paper II).

4 Influence of lesions in the autonomous nervous system on gastric secretion

Lesions in the autonomous nervous system have been demonstrated in diabetics (For literature, see Bárány and Cooper 1956; Root, 1959). Changes in the vasomotor, pilomotor and sudomotor innervation have been described. In the last two disorders at least, the lesion is of a post ganglionic nature (Bárány and Cooper, 1956) Neuropathy in the autonomous nervous system has also been mentioned as a cause of disturbance of gastro-intestinal function. It is possible that a diabetic neuropathy in the stomach may have an inhibiting effect on gastric secretion through reduction or extinction of the ner vous impulses to the secretory glands. Apart from this, there is reason to assume that the response of the secretory elements to humoral stimuli is also changed. According to Cannon's "Law of Denervation" an elimination of the peripheral neurone ought to cause the effector cells to become more sensitive to chemical stimuli (Cannon and Rosenblueth, 1949). Even if these conditions have been very little investigated as far as the gastric mucosa is concerned, there are grounds for believing that the Law of De nervation applies here also even though perhaps in a somewhat modified form and probably only for a short time (Muren, 1959 1961) On the other hand it has been found, at least in the case of the salivary glands (For literature see Emmelin, 1961), that denervation gives rise to a progressive atrophy of the glandular elements which implies that the maximal secretory capacity at any rate, diminishes. There are certain reasons for supposing that the same holds good of the gastric mucosa, but at present nothing can be said with any confidence. Where vascular supply is concerned, an in creased sensitivity towards the catechol amines circulating in the blood stream can be looked fo and this probably has a nega tive effect on the activity of the glandular elements

To sum up it may thus be stated that there are several possible reasons why dia betic neuropathy leads to a deterioration in the secretory capacity of all the secretory elements of the gastric mucosa.

a) elimination of the vagal stimulating effect, b) progressive atrophy of the glandular elements and c) progressive deterior ation of the blood supply to the glandular cells.

It seems likely that the combined in fluence of these factors at any rate in the long run, may predominate over some probably passing tendency to increased secretion which is occasioned by a sensitisation arising from denervation.

The effect of hyperglycaemia, on the other hand, has attracted less interest. That hyperglycaemia may inhibit the secretion of HCl is supported by previous investigations. A central and a peripheral effect have been envisaged. The former has been thought to be vagally conditioned and to be due to a diminished irritability in the secretory centre of the vagus nerve. The peripheral effect has been looked upon as a purely osmotic effect and not specific to glucose only (for literature, see Paper V). The effect of acutely induced hyperglycaemia on gastric secretion elicited by different methods of stimulation has been investigated in dogs with Pavlov or Heidenhain-pouches (Paper V).

Pavlov-pouch dogs

a. Teasing and sham-feeding

In both cases inhibition of gastric secretion was obtained even during the first 15 minutes of glucose infusion. As far as sham-feeding was concerned, at least, secretion began again 45–60 minutes after the completing of the glucose infusion.

b. Insulin stimulation.

Subcutaneous administration of 0.5 I.U. of insulin per kg body weight brought about a continuous secretion, which began about 1 hour after the injection, at a blood-sugar level of 50–60 mg%. When the secretion had become stabilised, infusion of glucose brought a substantial restriction in volume, even during the first period of 15 minutes, after which the secretion practically ceased. The acidity curve, also showed a steep drop downwards towards zero. After the infusion was completed, the blood-sugar value fell again, reaching hypoglycaemic values after 1 to 1½ hours. At a blood sugar level of 50–60 mg% gastric secretion recommenced, to cease once more when the blood-sugar had become normal 1½ to 2 hours after the completion of glucose infusion.

c. Feeding

In all experiments with Pavlov-pouch dogs, an inhibition of gastric secretion was obtained after feeding, on condition that glucose infusion was not given too long after the meal had been supplied.

Heidenhain-pouch dogs.

In Heidenhain dogs hyperglycaemia had little or no effect on the gastric secretion elicited by feeding. In no circumstances was the effect sufficient to provide any basis of comparison with the unmistakable effect in Pavlov dogs.

The results of the experiments with insulin stimulation demonstrate the necessity of a real hypoglycaemia to obtain a vagally elicited gastric secretion. Any swings of the blood-sugar value over the hypoglycaemia threshold value do not elicit a secretion. Hortmann (1946) arrived at the same result in his study of diabetes patients. In them also it was necessary to reach hypoglycaemia before the insulin had any stimulating effect on gastric secretion.

Experimental animal studies otherwise confirm that intravenous administration of glucose may inhibit gastric secretion. It seems to be principally the nervous phase which is involved, while the humoral effect is slight or completely absent. In the present investigations there is no evidence

6. Changes due to deficiency

The gastric mucosa is sensitive to various deficiency diseases which may lead to atrophic gastritis, usually of an irreversible nature.

It is well known that iron deficiency is often present with achlorhydria and hyposecretion of HCl. Wood and Taft (1958) are of the opinion that the gastritis is the primary factor and that the iron deficiency arises secondarily on account of reduced appetite and through small haemorrhages from the gastric mucosa. Witts (1959) on the other hand, thinks that, like glossitis and koilonychia, gastritis is a direct consequence of iron deficiency but differs from this in that it is usually irreversible. In diabetes too iron deficiency is probably not uncommon. Iron deficiency may therefore be connected in some way with the high incidence of achlorhydria and hyposecretion of HCl in diabetes. In Paper IV haemoglobin, serum iron, bone marrow examinations, and other factors bearing upon iron deficiency are studied in 10 diabetes patients with achlorhydria or hyposecretion of HCl. At least 2 of these patients had serum iron values at the lower limit and indications of iron deficiency in the bone-marrow. Five diabetic patients with normal HCl secretion showed no signs of iron deficiency.

Vitamin deficiency — particularly A and B avitaminosis — may also produce atrophic gastritis which may be reversible (for literature, see Schindler 1947). None of the patients in this investigation revealed any clinical signs of vitamin deficiency.

c. Histamine.

Gastric secretion elicited by histamine was not inhibited at all by glucose infused in the same quantities as had brought on the inhibition with, for instance, carbachol-stimulated secretion or that obtained after feeding in the case of Pavlov-pouch dogs (Fig. 2).

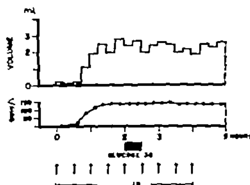


Fig. 2.
Effect of glucose infusion on the gastric secretory response to histamine.

Dotevall and Westling (1960) obtained similar results in experiments with histamine stimulation in human beings. Day and Komarov (1939) on the other hand, noted a certain (though very slight) inhibition in dogs, after injection of large quantities of glucose over a short space of time.

The investigations referred to above endorse the assumption that hyperglycaemia inhibits gastric secretion peripherally also. As in the experiments reported in Paper V glucose was administered in such quantities as to rule out any likelihood of an osmotic inhibition. The inhibiting effect was most pronounced with the secretion elicited by carbachol, but there was probable inhibition also with stimulation by mecholyl and urecholine. Carbachol in particular but also to a certain extent mecholyl and possibly in some degree urecholine, exercises an influence on the synapse. Histamine, on the other hand, has a more peripheral effect, in close connexion with or directly upon the secretory cell. The inhibitory effect of hyperglycaemia on gastric secretion, therefore, probably begins more proximally than the stimulating effect of histamine, and possibly wholly or partly upon the peripheral vagal synapse.

D. *Effect of long-standing hyperglycaemia on gastric secretion.*

The effect of long-standing hyperglycaemia on gastric secretion may be studied in experimental animals as well as in human beings. Investigations on dogs which were rendered diabetic by means of alloxan or by resection of the pancreas show at least in the case of Heidenhain-pouch dogs, an increased secretion of HCl (for literature, see Paper V). These experiments, however, occasioned complex changes in other organs, and it is not easy to draw any conclusions from the results obtained. The same objections apply in a certain degree to the study of the effect of hyperglycaemia on gastric secretion in patients with diabetes mellitus. It is probable that a number of factors contribute to the low secretion of HCl found.

It has been shown that the basal HCl secretion in diabetes is lower at blood-sugar values above 200 mg% than at values less than 200 mg% (Paper II). It might be

plications than in patients without such complications. The reason for this is probably reduced propulsive power due to pronounced degeneration in the wall of the stomach, with degenerative lesions not only in the nerve endings but also in the plexuses of the stomach.

Hypotony or atony of the stomach with retarded emptying as a result has been demonstrated in diabetes mellitus by means of X ray examination (for literature, see Paper III). The use of saline test-meals allows any insufficiency in the emptying mechanism of the stomach to be detected at an early stage, even before clinical symptoms reveal themselves. This is important in the treatment of various acute complications of diabetes, where a plentiful supply of liquid is necessary

Kassander (1958) has made a study of some diabetes patients with high-grade gastric atony whom he examined by means of X rays. For this disease-picture he has coined the expression *gastroparesis diabeticorum*

The connexion between gastric retention and diabetic diarrhoea has been discussed in Paper III. My opinion is that both diurnal and nocturnal diarrhoea may be caused by the collection of fermentation products and toxic matter in the stomach as a consequence of gastric retention. These substances may then have a locally irritating effect on the intestine, giving rise to hypermotility and diarrhoea.

tem. As for the pituitary gland hormones and the gastric mucosa, it has been shown that hypophysectomized cats develop an atrophy of the gastric glands which cannot be explained by diminished food intake (Haeger et al., 1953). Morphological changes occur in the parietal cells as well as in the chief cells and the volume of gastric juice and the amount of pepsin secreted are reduced (for literature, see Baker and Abrahams, 1955, Baker 1957).

In human beings, reduced gastric secretion has been reported in both Addison's and Simmonds' diseases (for literature, see Hunt, 1959). With treatment with ACTH and cortisone, on the other hand, the gastric secretion is augmented, particularly in the form of an increased peptic activity in the gastric juice (for literature, see Gray, 1959) but the secretion of HCl also rises (Clark et al., 1960).

In spite of clinical studies and studies carried out on experimental animals, the effect of the thyroid gland on gastric secretion is still unclear. It is known that HCl secretion is low in myxoedema and induced hypothyroidism (Card and Sircus, 1958, Sun et al. 1954). Treatment with thyroxine has an HCl-stimulating effect on patients with myxoedema (Card and Sircus 1958). In hyperthyroidism there is, according to Banti (1951), a "hyperacidity" during the early stages of the disease. Then hyposecretion of HCl or achlorhydria develops. The incidence of achylia varies between 34 and 68 % in different materials reported by Banti. Berryhill and Williams (1932), cited by Banti (1955) observed that HCl secretion returned when the hyperfunction of the thyroid gland ceased. In experimental animal studies of rats and dogs with intact pituitary function, thyroid hormones had an inhibiting effect on the secretion of HCl (Nasset et al., 1959, Goldsmith et al., 1959).

The part played by the pituitary gland in the metabolism of carbohydrates is of central importance. Both STH and ACTH have a diabetes-producing effect. In recent years, hypophysectomy has been carried out in malignant forms of diabetes in an attempt to bring about an improvement in the disease and its late complications. After complete hypophysectomy the insulin requirement decreases by more than 50 % (Luft et al., 1955).

C. *Gastric secretion of acid in man before and after hypophysectomy*

The effect of hypophysectomy*) on gastric secretion has been studied in accordance with the technique described in Paper II partly in diabetes patients and partly in patients with extensive cancer metastases, and a preliminary report has been given (Dotevall and Westling, 1959).

As the results obtained so far may be of interest for the elucidation of the cause of hyposecretion and achlorhydria in diabetes mellitus, data on 6 diabetes patients and 4 patients with cancer will be dealt with here.

a. Result

The result of the investigation of maximal histamine stimulation before and after

*) These studies have been carried out in collaboration with Dr. B. Sylvén, Medical Service II, and Dr. H. Westling, Department of Clinical Physiology, Sahlgren' Hospital, Göteborg.

Table 2. Functional and histopathological studies in four diabetic patients.

Case	Sex	Age Years	Dur of diabetes years	Insulin I.U./day	Max. hist. stim. Total HCl mEq/hour	Serum B_1 pg/ml.	Schilling test without intrinsic factor	Schilling test with intrinsic factor	Haemoglobin g/100 ml.	Serum iron μg per 100 ml.	Bone marrow	Gastric biopsy
R.A.	M	60	1	36	0	120	15.0 %		12.4	175	Normal	Atrophic gastritis
E.J	M	61	12	—	0	45	4.9 %	12.6 %	13.6	68	Normal	Atrophic gastritis
R.A.	M	55	20	60	0	—	8.4 %	11.5 %	9.2[1])	94	Sparse iron deposits	Atrophic gastritis
I.L.S.	F	31	15	92	0	320	18.8 %		10.4	35	Sparse iron deposits	—

[1]) The patient has haemorrhagic anaemia with BW + or (+).
X-ray examination of digestive tract shows normal conditions.

Table 1 Data on 6 diabetic patients studied with maximal histamine stimulation of gastric acid secretion after hypophysectomy

Case	Sex	Born	Age at onset of diabetes years	Age at hypophysectomy years	Late complications at time for hypophysectomy			Insulin treatment expressed in I U before and after hypophysectomy	
					Retinopathy	Nephropathy	Neuropathy	before	after
1	F	1927	9	32	+++	+	+	68	48
2	M	1926	17	33	+++	0	+	72	30
3	F	1927	13	32	+++	0	0	40	16
4	M	1928	11	31	+++	++	0	56	20
5	M	1930	3	26	+++	+	0	48	24
6	M	1928	6	29	+++	++	0	56	28

Retinopathy: +++ Haemorrhages with or without exudations and proliferative changes.
Nephropathy: + Urinary proteins < 0.2 %
++ 0.2 – 0.3 %.
Neuropathy: + Absent or weak muscular reflexes and/or loss of vibratory perception.

occurrence of pernicious anaemia — is raised. Tudhope, cited by Witts (1959), found 13 cases of pernicious anaemia among 116 patients with hypothyroidism. According to Witts (1959), the incidence of pernicious anaemia *is also higher* in thyrotoxicosis.

The combination of diabetes mellitus with pernicious anaemia was unknown up to 1910 (Parkinson, 1910) Right up to the 1940's their occurrence together was regarded as a rarity

The incidence of pernicious anaemia in different diabetes populations shows considerable variations on account of differences in the composition of the materials and in the times of the investigations. Between 1.5 and 10 cases of pernicious anaemia per 1 000 diabetics have been reported (for literature, see Paper IV and Panzram, 1960). In the material summarised in Paper I, the incidence was 11 per 1 000 in a diabetic material comprising 1,218 cases.

Even in a material of pernicious anaemia cases the incidence of diabetes shows great variation, from 3 to 82 diabetics per 1 000 pernicious anaemia patients (for literature, see Paper IV and Panzram, 1960).

In the materials studied during recent *years the simultaneous occurrence of diabetes* mellitus and pernicious anaemia seems to have increased. This is particularly the case with the occurrence of diabetes among patients with pernicious anaemia, for which Sundberg and Gröhberg *(1960)* give the figure of 6 7 and Panzram (1960) the figure of 8.2 The present investigations also make it seem likely that the incidence of pernicious anaemia in diabetes mellitus has risen. None of the incidence investigations of recent years supplies conclusive proof of this, however

The investigation reported in Paper II — with achlorhydria in 17% of the diabetics in a hospital material — renders it probable that the incidence of latent pernicious anaemia has also risen in diabetes mellitus. Even if the percentage figure for achlorhydria is not representative for an ordinary diabetic population, the investigation gives some support for a rise in the incidence of achlorhydria in diabetes. These results are to some extent contradicted by the investigations of Marks et al. (1959) who found 2 patients with achlorhydria according to Card and Sircus's criteria among 41 cases examined. The difference between the two investigations has been further *discussed in Paper II*

Panzram (1960) examined 400 diabetics by the desmoid method, and he states that 30 % of them had anacidity The incidence of anacidity was, however, as high in 200 control cases with heart and vascular disease. Tubeless investigation of gastric secretion is only of value, however as a screening test. In view of the technique employed and of the composition of his *control material, it is difficult to draw any* conclusions from these findings.

It is uncertain whether latent pernicious anaemia has any clinical significance in diabetes mellitus. There are, however, many features common to both diabetic neuropathy and pernicious neuropathy B_{12} deficiency as a partial cause of at least certain *forms of diabetic neuropathy should be*

responses occurred in several cases when a better control was obtained. Butterfield (1958), cited by Bech et al. (1960), measured the rate of blood flow plethysmographically and found it to be low in diabetics even with diabetes of short duration.

After a longer period of diabetes, there usually appear what have been called late diabetic complications, which manifest themselves clinically in particular in the eyes and kidneys. Histopathological studies of the late diabetic vascular changes in both these organs show that they are probably of the same nature (for literature, see Lundbaek, 1953). According to Lundbaek there is reason to assume a general vascular disease in diabetes mellitus: a diabetic angiopathy. During recent years diabetic vascular changes similar to those in the retina and kidneys have been met with in the vasa vasorum to the sural nerve (Fagerberg, 1959), in placenta vessels from diabetic mothers (Burstein et al. 1957), in the small vessels in the lower extremities (Goldenberg et al., 1959), and in intracranial vessels (Aronson and Aronson, 1960). The histopathological appearance in diabetic angiopathy has been discussed in Chapter V, page 28.

In Paper I the question was raised whether in diabetes mellitus there are not specific vascular changes in the gastric mucosa also. Angervall, Dotevall and Tillander (1961) later described similar vascular changes in the stomachs of diabetes patients in whom gastric resection had been carried out. In Paper IV is a report on stomach biopsies performed on diabetes patients, the specimens being examined for vascular changes, among other things. This investigation showed that vascular changes were found in all cases examined in which the patient had achlorhydria or hyposecretion of HCl after maximal histamine stimulation, but that they were also to be found in patients with normal HCl secretion.

B. The significance of diabetic vascular changes in the function of the gastric mucosa

As has been previously stated, Bárány (1955) and Sigroth (1957) have shown that vascular lesions may occur even at an early stage in diabetes. Histopathological studies of the gastric mucosa reported in Paper IV support this. Diabetic angiopathy has been demonstrated both with and without clinical late complications. The importance of these vascular changes during the early years of the disease is hard to judge. A more comprehensive study of the histopathology of the gastric mucosa in diabetes in correlation with diabetic late complications is in progress (Angervall, Dotevall, Fagerberg and Lehmann, in preparation), as are investigations dealing with non-diabetic stomachs with normal HCl secretion and with non-diabetic patients with atrophic gastritis. A preliminary account of the results obtained has already been presented (Angervall et al. 1961).

If it is applicable to the gastric mucosa, Bárány's theory involving diminished peripheral decomposition of catechol amines would explain — at any rate, in part — the reduced secretion of HCl in diabetics without clinical late complications. It has been shown by Harries (1956) in fact that nor-adrenaline has an inhibiting effect on gastric secretion. More advanced vascular lesions

CHAPTER V

The Histopathology of the Gastric Mucosa in Diabetes Mellitus

Biopsy of the gastric mucosa allows a small area of the stomach to be studied. As an isolated study this kind of investigation has only a limited value from the functional standpoint (Polmer and Spiro 1958). Combined with clinical functional tests, however histopathological studies of the gastric mucosa may give essential informations. Mucosal biopsy is principally employed for the examination of the tunica mucosa, but also in certain cases, parts of the tunica submucosa are examined by this means. The mucosal biopsies reported in Paper IV were taken from the body of the stomach. The specimens were examined for signs of inflammatory changes, vascular changes glandular atrophy and metaplasia.

1. Inflammatory changes

From the histopathological point of view gastritic changes often occur independently of clinical symptoms. Lykke-Olesen (1960) investigated the incidence of gastritis in clinically healthy stomachs and found histological signs of inflammatory changes in 80 of the cases. Where diabetes is concerned, Joske et al. (1955) state that gastritis is common. Studies described in Paper IV show that all but two of the diabetes patients examined had gastritis The clinical significance of gastritis for gastric secretion has been discussed in Chapter II page 19

2. Changes in glandular structure

At the same time as high-grade inflammatory changes, there occur metaplastic and atrophic changes among glandular elements. As is shown in Paper IV the clinical functional tests, and particularly maximal stimulation of gastric secretion by histamine, are in good correlation with the histological changes All the patients examined who had achlorhydria or pronounced hyposecretion (total HCl < 5 mEq/hr) showed histologically the presence of an atrophic gastritis, while the patients with normal HCl secretion showed no atrophic changes. The material described in Paper IV and Table 2 has now been enlarged, and the result does not *substantially* deviate from previous experience (Angervall, Dotevall, Fagerberg and Lehmann, in preparation)

3. Vascular changes

Histopathological studies of the small vessels in diabetes mellitus reveals features, which are more common and possibly differ from non-diabetic vessel changes. The specimens are characterised by a deposit of abundant so called "PAS—positive" material in the wall (staining with periodic acid Schiff stain — after McManus 1948), thickening of the walls, calibre reduction, and endothelic proliferation. (For further literature, see

5. Influence of inflammatory changes in the gastric mucosa on gastric secretion

According to Teorell (for literature, see Teorell, 1947 Heinz and Öbrink, 1954) changes in the acidity of the stomach are regulated by means of diffusion and exchange of hydrogen ions for sodium ions. The following factors affect this diffusion:

the concentration gradient between tissue fluid and gastric juice,

the diffusion area,

the volume of gastric contents, and

the permeability of the mucosa.

Teorell's diffusion theory has received confirmation in a number of investigations (Ihre, 1938, Elliot et al., 1942; Tamant and Salamanca J., 1951). Hunt (1959) writes: "The question of the moment is not 'does instilled acid diffuse and exchange?' but 'to what extent does secreted acid diffuse back across the secreting gastric mucosa under various normal circumstances'".

Ihre (1938) has indicated the possibility that the low acidity in patients with gastritis may be due to an increased reabsorption of hydrogen ions in the first place caused by an increase in blood-flow in the gastric mucosa.

As has been mentioned, it has been shown that diabetics have a high incidence of gastritis in investigations by means of stomach biopsy also (Joske et al., 1955) (Paper IV) Chronic gastritis, with or without vascular changes, may of course directly affect and destroy the secretory cells of the gastric mucosa, with a diminished secretion of HCl as a result.

An increased exchange of hydrogen ions for sodium ions in diabetes would partly explain the high incidence of achylia and hyposecretion, but it would have given a higher value for the expected secretion of non-parietal component, that is, a lower acidity

In order to elucidate whether an increased reabsorption of hydrogen ions in exchange for sodium ions occurs in diabetes mellitus the effect of introducing acid into the stomach has been investigated in a control material and in diabetic patients (Doterall, 1961). 30 mEq/l sulphuric acid in a 5° sucrose solution was employed. Determination of sodium, potassium and chlorides in the gastric contents was carried out. The control cases consisted of 15 persons (the same as in Paper III). The diabetics consisted of 13 patients of whom 10 were without late complications and 3 with. The output of sodium was calculated by the same method as for hydrogen ions in Paper III the method used by Hunt. The output of sodium after the administration of 30 mEq/l hydrogen ions was the same for control subjects and diabetic patients. The results obtained are against the explanation that diabetics have an increased reabsorption of hydrogen ions in exchange for sodium ions in spite of gastritis. The cause of this may possibly be ascribed to degenerative changes in the gastric mucosa particularly diabetic angiopathy which reduces the possibility of reabsorption of hydrogen ions and their exchange for sodium ions owing to reduced circulation

General summary

Chapter I The incidence of ulcer in a diabetic material was investigated. Out of 1,218 diabetics, 22 patients had peptic ulcer during the course of the diabetes, 9 of these being duodenal and 13 gastric ulcer cases. The proportion of duodenal to gastric ulcers in different control materials varies between 1,3 and 7 7 The corresponding proportion in the present diabetes material was 0 7 A statistical computation for a control material of the same composition gave an expected incidence of 33 cases of duodenal ulcer and 13 of gastric ulcer. Thus the under representation in the present diabetic material referred only to patients with duodenal ulcer. Possible reasons for this are discussed.

Chapter II: Gastric secretion of acid was studied in a diabetic material and in a control material. In both males and females, the basal secretion of HCl and secretion after maximal stimulation with histamine were lower in diabetics than in control cases. Various possible causes of this low HCl secretion were investigated.

1) Hyperglycaemia and gastric secretion.

The effect of the intravenous administration of glucose was studied in dogs equipped with Pavlov or Heidenhain pouches. In Pavlov-pouch dogs a pronounced inhibition of the secretory response was observed during sham feeding o teasing with food. The response to feeding was also temporarily depressed, at least during *the first two hours after feeding* In Heidenhain dogs, the response to feeding, in comparison to that of the Pavlov dogs, was hardly affected significantly except during special conditions. It is suggested that the induced hyperglycaemia mainly depresses the nervous phase of secretion, both at the central and at the peripheral levels.

The peripheral effect of hyperglycaemia on gastric secretion was investigated in dogs by studying the secretion elicited by carbachol, mecholyl, urecholine and histamine. The secretion elicited by carbachol in particular — but possibly also that elicited by mecholyl and urecholine — was inhibited by intravenous administration of glucose, while that elicited by histamine was not affected. The peripheral inhibitory effect of hyperglycaemia begins more proximally than the stimulating effect of histamine, and possibly wholly or partly upon the peripheral vagal synapse.

2) Endocrine factors and gastric secretion.

A brief review of the general influence of endocrine factors on gastric secretion is given. Maximal stimulation of gastric secretion by histamine was carried out on diabetes and cancer patients before and after hypophysectomy After complete hypophysectomy with cortisone substitution only the HCl secretion expressed in mEq/hr decreased by an verage of 50% This tallies with previous experiences in the case of animals. In diabetes patients who after hypophysectomy were given cortisone and thyroid hormone substitution treatment if *indicated, a significant rise in HCl secretion* was obtained after maximal stimulation

CHAPTER III

Gastric Motility and Emptying in Diabetes Mellitus

Although gastric emptying may occur in the apparent absence of peristalsis — that is a wave of constriction seen radiologically to pass along the gastric axis — there is little doubt that peristalsis is responsible for the main part of the transfer of the gastric contents to the duodenum (Hunt, 1959). Usually about three to four peristaltic waves per minute course over the gastric antrum (Jungmann and Venning, 1952) and result in ejections of the gastric contents into the duodenum.

Since the rate of emptying of gastric contents with ordinary food is usually about 500 ml per hour and three to four peristaltic waves per minute the "stroke volume of the gastro-duodenal pump" is not more than 3 ml (Hunt, 1959). Distension of the stomach is the only natural stimulation activating gastric emptying (Hunt and MacDonald, 1954). Inhibition of emptying on the other hand, is governed by receptors located in the duodenum and the upper part of the jejunum (for literature, see Hunt, 1959).

In the work presented in Paper III, gastric emptying was studied in control cases and in diabetics with and without clinical late complications, with test-meals consisting of 100 mEq NaCl per litre and test-meals consisting of 30 mEq H per litre in 5 sucrose solution. The first test meal leaves the stomach very rapidly because of minimal inhibition. Its rate of emptying is regarded as a measure of the propulsive power of the stomach (Hunt, 1958). The second test-meal, on the contrary is subjected to inhibition from receptors in the duodenum and jejunum, and therefore leaves the stomach more slowly.

1. Gastric emptying in diabetics without clinical late complications

With saline test meals, diabetics without clinical late complications have a higher rate of emptying than diabetics with late complications and control cases. A possible explanation of this is the lower secretion of HCl in diabetics as compared with control cases with reduced inhibition as a result. In favour of this theory to some extent, is the fact that there was no statistically significant difference in the rates of emptying of these two groups when test-meals containing acid in sucrose solution were administered. Another possibility is that diabetics without late complications are less sensitive to the minimal stimulating properties of saline test-meals than are controls which results in a more rapid emptying on account of reduced inhibition. The cause of such a diminished sensitivity may be degenerative changes in the nerve endings in the intestinal wall which are either primary or else secondary to diabetic angiopathy (see page 28).

2. Gastric emptying in diabetics with clinical late complications

Gastric emptying with saline test-meals is slower in diabetics with clinical late com

the present study also that the incidence of pernicious anaemia has risen in diabetics.

Chapter V: Biopsy of the gastric mucosa was performed on diabetes patients with normal HCl secretion and hyposecretion, and on patients with achlorhydria. Patients belonging to the first group showed no histopathological signs of glandular atrophy. The last two groups, on the other hand, presented varying degrees of atrophic gastritis with considerable reduction or total absence of glandular elements. Histopathological studies of vessels in diabetes patients revealed in the majority of cases an appearance that is possibly characteristic of diabetics.

CHAPTER IV

Gastric Secretion of Intrinsic Factor and Pepsin in Diabetes Mellitus

1. Gastric secretion of intrinsic factor and pepsin in achlorhydria and atrophic gastritis

Functionally the gastric mucosa is composed of the pyloric gland area and the corpus or gland area proper. The latter consists of parietal cells, which secrete HCl, zymogenic cells, which secrete pepsin; and mucoid cells which probably secrete intrinsic factor. Gastric juice secreted on stimulation by histamine is richest in HCl, but also contains pepsin and intrinsic factor. Stimulation by insulin and [illegible] choline esters on the other hand, gives a gastric secretion rich in pepsin and intrinsic factor.

Degenerative changes in the gastric mucosa with progressive glandular atrophy results in the disappearance of acid, pepsin and intrinsic factor, in that order (Witts, 1932; Poliner and Spiro 1958 Callender et al. 1960). Exceptions to this rule are found (see Callender et al. 1960; Siurala et al., 1960). In looking for deficiency of intrinsic factor the presence of achlorhydria may be used as a screening test. After the introduction of the augmented histamine test achlorhydria has turned out to be much rarer than had been thought previously. Card and Sircus (1958) define achlorhydria as "the state of gastric secretion in which, under the conditions of the test, the pH of the secretion fails to fall below 6.0". Callender et al. (1960) use the term achlorhydria when the pH of the gastric juice does not fall below 3.5 and does not change towards acidity by more than 1 unit after maximal histamine stimulation.

Out of 500 patients Card and Sircus (1958) found achlorhydria after maximal histamine stimulation only in those patients who turned out to have pernicious anaemia. Retief (1959) examined by the augmented histamine test 128 patients who had been diagnosed as achlorhydria cases by means of gruel or single histamine test meal or the diagnex test. He found achlorhydria in 31 cases. Of 24 patients with complete achlorhydria, 10 showed lowered absorption of radioactive Vitamin B[illegible]. In the majority of these patients the serum B[illegible] was below the normal level. Witts (1960) has introduced the notion of latent or subclinical pernicious anaemia for patients with defective secretion of intrinsic factor without clinical signs of anaemia. He speaks of pernicious anaemia as an "iceberg phenomenon, with only ⅙ visible above the water-line" this visible portion being manifest pernicious anaemia, while the submerged portion consists of latent pernicious anaemia.

Paper II is a report of maximal histamine stimulation carried out on 60 patients with diabetes mellitus. Of these 10 had achlorhydria according to the criteria of Card and Sircus. Six of these patients, together with 1 patient with manifest pernicious anaemia and diabetes, were further examined (Paper IV) with respect to uropepsin, serum B_{12},

REFERENCES

1. Angervall, L., Dotevall, G. Fagerberg, S.-E. & Lehmann, K.-E. The gastric mucosa in diabetes mellitus. Acta. Path. Microbiol. Scand. In press, 1961

2. Angervall, L., Dotevall, G. & Tillander, H. Amelioration of diabetes mellitus following gastric resection. Acta Med. Scand. *169* 743, 1961

3. Aronson, S. M. & Aronson B. E. Intracranial vascular lesions in diabetes mellitus. J Neuropath. *19*: 152, 1960.

4. Baker, B. L. The influence of the hypophysis and adrenals on digestive function. Amer. J. Clin. Nutr. *5* 445 1957

5. Baker, B. L. & Abrahams, G. D. Growth hormone and the glands of the digestive system. In Smith, R. W., Gaebler, O. H. & Long, C. N. H. The hypophyseal growth hormone nature and actions. International Symposium. M. Graw-Hill Publ. Company Ltd New York, Toronto, London 1955.

6. Bansi, H. W. Krankheiten der Schilddrüse. In Handbuch der Inneren Medizin VII. Editores G. v. Bergmann, W. Frey & H. Schwiegk. Springer Verlag. Berlin, Göttingen, Heidelberg 1955.

7. Bárány F. R. Abnormal vascular reactions in diabetes mellitus. Acta Med. Scand. Suppl. *304* 1955.

8. Bárány, F. R. & Cooper, E. H. Pilomotor and sudomotor innervation in diabetes. Clin. Sci. *15* 533, 1956.

9. Bech, K., Hansen, B. S., Lorentzen, S. E. & Lundbaek, K. The V/A ratio of the smaller vessels of the bulbar conjunctiva in diabetes mellitus. Diabetes *9* 441 1960.

10. Burstein, R., Blumenthal, H. T. & Soule, S. D. Histogenesis of pathological processes in placentas of metabolic disease in pregnancy II. The diabetic state. Am. J. Obst. and Gynec. *74* 96 1957

11. Callender, S. T. Retief F. P. & Witts, L. J. The augmented histamine test with special reference to achlorhydria. Gut *1* 326 1960.

12. Cannon, W. B. & Rosenblueth, A. The supersensitivity of denervated structures. New York 1949

13. Card, W. I. & Sircus, W. Anacidity. In F. Avery Jones: Modern trends in gastroenterology. Second series. Butterworth and Co London 1958.

14. Clarke, S. D. Neill, D. W. & Welbourn, R. B. The effects of corticotrophin and corticoids on secretion from denervated gastric pouches in dogs. Gut, *1* 36 1960.

15. Day J. J. & Komarov S. A. Glucose and gastric secretion. Amer. J. dig. Dis. *164* 463 1939

16. Dotevall, G. Ingestion of hydrogen ions in the stomach of man. In preparation, 1961

17. Dotevall, G. & Muren, A. Effect of intravenous infusion of glucose on gastric secretory responses to different chemical drugs. In preparation.

18. Dotevall, G. & Westling, H. Gastric secretion of acid in man before and after hypophysectomy. Lecture to the Swedish Society of Gastroenterology Goteborg 1959

19. Dotevall, G. & Westling, H. On the effect of glucagon on histamine-induced and spontaneous gastric acid secretion in man. Scand. J. Clin. Lab. Invest. *12* 489 1960.

20. Elliot A., Rehholm, L. & Öbrink, K. J. Exchange diffusion of hydrochloric acid through gastric mucosa in man. Acta Med. Scand. *110* 267 1942.

21. Emmelin, N. Supersensitivity following "pharmacological denervation. Pharmacol. Rev *13* 17 1961

22. Fagerberg, S. E. Diabetic neuropathy. A clinical and histological study on the significance of vascular affections. Acta Med. Scand. Suppl. *345* 1959

23. Goldenberg, S., Alex, M., Joshi, R. A. & Blumenthal, H. Nonatheromatous peripheral vascular disease of the lower extremity in diabetes mellitus. Diabetes *8* 261 1959

Schilling test, serum iron, stomach biopsy and morphological studies of the bone marrow. After the investigation was completed, 1 more patient belonging to this group was partially examined. In addition, 3 cases of complete achlorhydria were met with among 10 other diabetes cases under hospital care. The results of the examinations of these patients are set out in Table 2. Of the 10 patients thus investigated 3 showed defective secretion of intrinsic factor (Cases 2 and 3 Paper IV Case E. J Table 2). A new Schilling test with intrinsic factor in Case 3 Paper IV showed a value of 15 7

One patient (Case 4 in Paper IV) with hypothyroidism, under treatment with thyroxine, is a borderline case. Another patient (Case R. A. in Table 2) shows only a slight increase of Schilling test on simultaneous administration of intrinsic factor. This may be due as much to defective secretion of intrinsic factor as to disturbance of intestinal absorption.

Uropepsin values are looked upon as measure of the secretion of pepsin by the gastric mucosa. The majority of patients with achlorhydria had low values of uropepsin, while the uropepsin excretion was not reduced with hyposecretion or normosecretion of HCl.

The histopathological picture of the gastric mucosa in patients with achlorhydria given in Paper IV and Table 2 agrees with the investigations of Retief (1959), who found atrophic gastritis or glandular atrophy in 22 of the 29 cases he examined. Since the publication of the account of the investigation in Paper IV Callender Retief and Witts (1960) have given a report on a large group of patients with achlorhydria based on Retief's earlier investigations. Out of 136 patients examined, with different basic diseases (diabetes mellitus was not included in their material) and achlorhydria demonstrated by means of previous test-meals 31 had true achlorhydria after the augmented histamine test. Of these patients, 38 had an absorption of Co—B of less than 40 of the quantity administered, 54 had Vitamin B in serum less than 150 pg ml, and 80 had uropepsin less than 50 μg 24 hrs. Siurala et al. (1960) have made corresponding studies of patients with severe atrophic gastritis and found in 70 Schilling test below 10 in 64 a serum B value below 150 pg ml, and in 95 a pathologically low value of uropepsin.

2. Manifest and latent pernicious anaemia in diabetes mellitus

The incidence of pernicious anaemia varies considerably in different parts of the world. It is common in the white races but practically non-existent in Japan, for instance. In England, Scott (1960) reports an incidence varying between 0,85 and 1,84 per 1 000. Corresponding figures for the population of a Swedish county were 1,2 to 1,5 per 1 000 (Waldenström, 1947). Witts (1960) calculates the incidence of pernicious anaemia in the over-40 population of England to be about 2,5 per 1 000

The connection between achlorhydria, pernicious anaemia and endocrine disturbance is still obscure. With thyroid diseases the incidence of achlorhydria — like the

51 SIPLEY H. & GAUEN-
experimental athyrol-
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roenterology 27 189

52 ...AO, A. Diabetes melli-
mis. Acta Med. Scand.

53 ...MANCA, JR. F H.: La
mucosa gástrica. Arch.
1

54 diffusion in relation to
gastric juice. Gastro-
7

ence of peptic ulcer in
2. Acta Med. Scand.

55 ...ehandlinger vid leverbe
Nord. Med. 16 3208

56 ...logy and treatment of
...oietic anaemias. Lan-

57 ...nth Francis Shepherd
...chydria and anaemia.

58 1959
...opment of pernicious
24 1 1960.

59 L. Diffuse lesions of
Arnold, 1958.

60 ...LSON, E. H. Primary
...e jejunum associated
of the pancreas. Ann.

taken into consideration, even at normal blood values and normal morphology of the bone marrow and perhaps also at serum B_{12} values within the current normal limits

3. Influence of the endocrine system on the secretion of intrinsic factor

As mentioned in Chapter II gastric secretion is affected in a high degree by endocrine factors. Of the diabetics, as may be seen in Fig 3 one patient with true achlorhydria and one with hypochlorhydria (fall in pH from 6.2 to 4.8 corresponding to about 0.05 mEq/hr) after maximal histamine stimulation were examined before and after hypophysectomy After hypophysectomy and substitution therapy (see page 13) the HCl secretion rose to 14.2 mEq/hr and 3.7 mEq/hr respectively Unfortunately neither of these patients was further examined with respect to intrinsic factor and Vitamin B_{12} In spite of this, the result would seem to be of great theoretical interest in that, to my knowledge there is nothing to be found in the literature about a return of HCl in achlorhydria proved by the augmented histamine test.

It is possible, however that treatment with corticosteroids affects the formation of intrinsic factor. Gordin (1959) studied pernicious anaemia patients by means of the Schilling test before and during treatment with corticosteroids. He found a significant increase in the absorption of Vitamin B in patients who had not undergone stomach resection.

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Lundbaek 1953 Fagerberg 1959· Goldenberg 1959).

In resection material from diabetic stomachs Angervall, Doterall and Tillander (1961) have found vascular changes of the kind described above. Blood vessels in stomach biopsies from patients with diabetes reported in Paper IV also show a similar histopathological appearance. The functional significance of these vascular changes has been discussed in Chapter II page 16

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with histamine. The possibility that the pituitary gland may also have an inhibiting effect on HCl secretion is discussed

3) Blood vessel changes and gastric secretion.

The reduced HCl secretion found in diabetes mellitus has been associated with degenerative changes in the gastric mucosa. Patients with clinical late complications showed lower HCl secretion after maximal histamine stimulation than patients without late complications. Diabetic angiopathy has been met with in histopathological studies both of patients with clinical late complications and of patients without. The connexion between vascular lesions in early stages of diabetes and histologically demonstrable angiopathy is discussed.

4) Nervous changes and gastric secretion

A review of the influence of diabetic neuropathy on gastric secretion is given. Elimination of the vagal stimulation, progressive atrophy of glandular elements and progressive deterioration of the blood supply to the glandular elements as a result of neuropathy may lead to a reduced capacity of the secretory glands of the gastric mucosa.

5) Other factors which are possible contributory causes of the low HCl secretion in diabetes mellitus are discussed. These include such factors as inflammatory changes in the gastric mucosa and various deficiency diseases.

Chapter III: Gastric emptying was studied in diabetics and control cases after a method described by Hunt and Spurrell. Investigation by means of saline test-meals showed a higher rate of emptying in diabetics without clinical late complications than in control cases and in diabetics with late complications. One of the causes of this may be a reduced inhibition owing to lower HCl secretion in the diabetes group. Another possibility is a reduced inhibition due to degenerative changes in the nerve endings in the wall of the intestine. Diabetics with pronounced clinical late complications had a lower rate of emptying than diabetics without late complications and control cases. The reason for this is probably progressive lesions in the stomach with degenerative changes not only in the nerve endings in the digestive tract but also in the plexuses of the stomach.

Chapter IV: 17   of the diabetes patients examined with maximal histamine stimulation had achlorhydria. The majority of these patients were further examined with regard to haemoglobin, serum iron, serum B   Schilling test, and morphological studies of the bone marrow. Approximately the same number of patients with latent pernicious anaemia and various transitional forms of the disease were met with in this group as in non-diabetic achlorhydria materials of which accounts had previously been published. The connexion between latent pernicious anaemia and diabetes mellitus is treated.

According to reports in recent years, the occurrence together of diabetes mellitus and pernicious anaemia has become more frequent. This applies particularly to the occurrence of diabetes among patients with pernicious anaemia. It seems probable from

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GOLDSMITH, D. P. & N... E. S. Relation of thyroid to gastric secretion in the anesthetized cat. Amer. J. Physiol. *197* 1 1959

25. GORDIN R.: Vitamin B_{12} absorption in corticosteroid-treated pernicious anaemia. Acta Med. Scand. *164* 159 1959

26. G... S. J. Present status of endocrine influences upon the stomach and their relationship to peptic ulcer disease. Proc. of the World Congress of Gastroenterology 396, 1958. The Williams and Wilkins Company Baltimore 1959

27. GREGORY R. A. T... H., FRENCH, J. M. & SIRCUS, W. Extraction of gastrin-like substance from pancreatic tumour in case of Zollinger Ellison syndrome. Lancet *1* 1045 1960

28. HALLGREN K., JACOBSSON, D. & KARLSSON, G. Atrophy of the gastrointestinal mucosa following hypophysectomy or adrenalectomy. Acta Physiol. Scand. Suppl. 111 p. *141* 1953

29. HARRIES, E. H. L. The effect of noradrenaline on the gastric secretory response to histamine in the dog. J. Physiol. (Lond.) *133* 498 1956.

30. HEINZ, E. & OBRINK, K. J. Acid formation and acidity control in the stomach. Physiol. Rev. 34 643 1954.

31. HORNE... P. Blodsukker og ventrikelsekretion. En klinisk-eksperimentel studie. Einar Munksgaard København 1946.

32. HUNT J. N. Regulation of gastric emptying. In Modern trends in gastroenterology (2nd ser.) edited by F. A. Jones. Butterworth, London 1958

33. HUNT J. N. Gastric emptying and secretion in man. Physiol. Rev. *39* 491 1959.

34. HUNT J. N. & MACDONALD I. Influence of volume on gastric emptying. J. Physiol. (Lond.) *126* 459 1954

35. HUNT J. N. MACDONALD, I. & SPURRELL, W. R. The gastric response to pectin meals of high osmotic pressure. J. Physiol. (Lond.) *115* 185 1951

36. IHRE, B. Human gastric secretion. Acta Med. Scand. Suppl. *95* 1938.

37. JOYCE, R. A., F..., E. S. & WOOD I. J. Gastric biopsy. Study of 1,000 consecutive successful gastric biopsies. Quart. J. Med. *4* 269 1955

38. JENSEN... H. & ..., P. Some data on the normal variation of the stomach observed radiologically. Brit. J. Radiol. *25* 23 195..

39. KASSANDER, P. Asymptomatic gastric retention in diabetics (Gastroparesis diabeticorum). Ann. Int. Med. *48* 797 1958.

40. LUFT R., OLIVECRONA, H. & SJÖGREN B. Hypophysectomy in man. Experiences in severe diabetes mellitus. J. Clin. Endocrinol. *15* 391 1955

41. LUNDBAEK, K. Long-term diabetes. Munksgaard, Copenhagen 1953.

42. LYKKE-OLESEN, O. Gastritis in clinically healthy stomachs. Einar Munksgaard Ltd, Copenhagen 1960

43. MACMANUS, J. F. A. Histological and histochemical uses of periodic acid. Stain. Technol. *23* 99 1948.

44. MARKS, I. N. SHUMAN C. R. & SHAY H. Gastric acid secretion in diabetes mellitus Ann. Int. Med. *51* 227 1959

45. MOLLER, A. Effect of vagotomy on the secretory responses of the Pavlov pouch to mecholyl and histamine. J. Physiol. (Lond.) *149* 70 P 1959

46. MOLLER, A. Effect of vagotomy on gastric secretory responses to mecholyl and histamine. In manuscript.

47. NASSET E. S., LOGAN, V. W. KELLY M. L. & THOMAS, M. Inhibition of gastric secretion by thyroid preparations. Amer. J. Physiol. *196* 1262, 1959

48. OBERHELMAN, H. A. & DRAGSTEDT L. R. Effect of vagotomy on gastric secretory response to histamine. Proc. Soc. Exp. Biol. *67* 336 1948.

49. PAGLIARA, G. Peroxidase Aktivität und Diabetes Mellitus. Z. ges. inn. Med. *5* 239 1960.

50. PAGLIARA, G. Die Häufigkeit der Anazidität des Magensaftes beim Diabetes Mellitus. Dtsch. Ges. Wesen. *15* 116 1960

Chemical Carcinogens

Dr W Carruthers,
Carcinogenic Substances Research Unit, Exeter Great Britain

It is now just thirty years since the first pure synthetic chemical carcinogens were prepared and tested in the late Sir Ernest Kennaway's laboratory in London. These substances belonged to the chemical class of polycyclic aromatic hydrocarbons and since that time many hundreds of other carcinogens of a variety of chemical types have been discovered. The latest edition of Hartwell's Survey of Compounds which have been Tested for Carcinogenic Activity which with its Supplement covers the period upp to 1953 records tests on 2310 substances, of which 511 caused malignant tumours. There is no reason to think the list is complete.

Kennaway's discovery had its origin in a much earlier observation by the English physician, Percival Pott, who in 1775 described a form of scrotal cancer common among chimney sweeps. He clearly recognised the disease as a form of industrial cancer and ascribed it to the action of the soot to which the sweeps were exposed in the course of their work. Round about the beginning of this century other cases of industrial skin cancer were recognised among coal tar workers, in employees in the Scottish shale industry especially those engaged in wax pressing and among mule spinners in the Lancashire cotton industry These cancers also were ascribed to the effect of the coal tar and mineral oil fractions with which the men came into contact.

All attempts to show that these materials were indeed carcinogenic by experiments on animals were unsuccessful, however until 1915 when the Japanese pathologist Yamagiwa produced cancer experimentally for the first time by prolonged application of coal tar to the ears of rabbits. A few years later his countryman Tsutsui showed that coal tar could also cause skin cancer in mice. This discovery gave a great impetus to experimental cancer research. A method of testing active fractions was now available and this technique of application to the skin of experimental animals has been extensively used ever since in testing for carcinogenic activity For example Passey in 1922, obtained malignant tumours on mouse skin by application of an ethereal extract of soot, thus demonstrating the carcinogenic action of soot, and vindicating the view put forward by Percival Pott nearly 150 years before

Kennaway and others used the technique in their investigations of the carcinogenic action of coal tar Coal tar and mineral oils are complex mixtures and it was obviously important to determine which of their constituents were responsible for their carcinogenic action. Bloch had shown that the active constituents of tar were in the high boiling fractions, and Kennaway was able to prepare other carcinogenic tars by pyrolysis of various organic materials, including acetylene and

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Plac	*3 4 Ben pyren µg/100 m³*
Beckton	7 1
London County Hall	4.6
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Oslo	0 6
Bergen	1.2[1]
Reykjavik	0.25[2]

Aver g Annual Amou t f 3 4-benzpyrene in th ar of British and S andinavian Towns (fter Doll) [1] Winter aver g [2] Summer averag

The benzpyrene concentrations vary greatly from one city to another and are highest in large industrial cities. The Scandinavian cities have very low values compared with London and Liverpool. It has been suggested that the higher incidence of lung cancer among city dwellers compared with those who live in the country may be related to the contamination of city atmospheres with benzpyrene and other carcinogens. It has been known for some years that atmospheric dust is carcinogenic to experimental animals.

Aromat hyd oca b ns

A large number of other polycyclic aromatic hydrocarbons has now been prepared and tested for carcinogenic activity and they form a considerable proportion of th five hundred or so carcinogenic compounds which are known. Many of the active hydrocarbons are deri atives of 1 2-benzanthracene III) which has been more intensi el studied than other aromatic systems

The parent h drocarbon 1 2 benzanthracene is itself nactive or only ery slightly active but bstitution of methyl groups in suitabl p tions gives rise to substances with carcinogenic properties. A very great deal of work has been done on the effect of different substituent groups on the carcinogenic activity of benzanthracene derivatives. In general, introduction of a methyl group into any posi tion in the anthracene nucleus results in development of activity and positions 5- 9- and 10- appear to be particularly favourable for this. Thus 6- methyl 1.2-benz anthracene (IV) is a weak carcinogen but the 10-methyl derivative (V) is a moderately active compound. Introduction of a second and third methyl group leads in general to a further increase of activity 9 10-Dimethyl-1.2-benzanthracene (VI) which has a methyl group in two of the "favourable" positions is an extremely potent carcinogen and has produced tumours in mice after an average latent pe riod of only 43 days.

5:9 10- (VII) and 6:9 10- Trimethyl benzanthracene are also very active compounds, but the 6 7-dimethyl derivative (VIII) which does not have a substituent in one of the "favourable" positions is only a weak carcinogen. There is apparently a limit beyond which further substi tution no longer leads to an increase in activity 5·6:9 10-Tetramethyl-1:2-benz anthracene (IX) for example, is less carcinogenic than the trimethyl derivatives to which it is related. It is clear that the activity of benzanthracene derivatives is in some way related to the structure of the compound and very minor altera tions in structure can in some cases lead to complete loss of activity Thus, all the derivatives substituted in the angular ring which have so far been tested have been found to be inactive e.g (X)

Replacement of a methyl group in an acti e compound by larger alkyl groups leads to reduction or loss of activity Thus 10-ethyl 1 2-benzanthracene is less active than the 10-methyl compound, and higher

Symposium on
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L. HJERN
Editor

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The Tobacco Research Committee of the Swedish Medical Research Council

homologues are inactive. Other substituents lead to less predictable results. Carcinogenic derivatives are known with both electron-attracting and electron repelling substituents, for example, 10-methoxy-and 10-cyano-1.2-benzanthracene are both active. Other substituents lead to loss of activity notably the hydroxyl group e.g. 10-hydroxy 1 2-benzanthracene is completely inactive.

Carcinogenic activity in the aromatic hydrocarbon series is not confined to derivatives of 1.2-benzanthracene. Another important ring system is 3·4-benzphenanthrene (XI) The parent compound itself is weakly active to the skin of mice and once again introduction of methyl groups, particularly in the 1 and 2-positions, results in an increase of activity 2 Methyl-3·4-benzphenanthrene (XII) is a moderately potent compound.

Again chrysene (XIII) is only very weakly active it has given a few sarcomas by injection in mice. But the 1 methyl and 1.2-dimethyl (XIV) derivatives are moderately active.

Among the more complex hydrocarbons 1.2 .5·6-dibenzanthracene (I) and 3·4 benzpyrene (II) were shown to be active in the early studies of carcinogenic hydrocarbons. 1:2 .5·6-Dibenzanthracene was the first pure synthetic substance shown to be carcinogenic and it is interesting that the isomer 1.2 7.8-dibenzanthracene (XV) is only very feebly active and 1.2 .3·4-dibenzanthracene (XVI) appears to be inactive. 1.2 .5·6-Dibenzphenanthrene (XVII) and 1 2 3·4-dibenzphenanthrene (XVIII) are moderately active. Recently Wynder and Hoffman have found that benz (b) flouranthene (3·4-benzflouranthene) (XIX) and benz (j) flouranthene (10 11-benzflouranthene) (XX) are fairly potent carcinogens to mouse skin and they have detected the hydrocarbons in cigarette smoke. Among the hexacyclic compounds, 1.2 3·4 (XXI) 3·4 :8:9-(XXII) and 3·4 :9 10- (XXIII) dibenzpyrenes are all powerful carcinogens. Each of these hydrocarbons is said to have been detected in cigarette smoke.

Hydrocarbon Carcinogens as derivatives of phenanthrene

Many attempts have been made to relate the activity of hydrocarbon carcinogens to their structure. Hewett has pointed out that many of the most active aromatic hydrocarbon carcinogens can be regarded as substituted phenanthrenes in which three or four of the positions 1,2,3 4 are substituted by methyl groups or a benzene ring

Thus 1.2-benzanthracene can be considered as 2.3-benzphenanthrene and if methyl groups are introduced at the 1 and 4 positions carcinogenic hydrocarbons are produced. For example 1 methyl-2 3-benzphenanthrene is 10-methyl 1:2-benzanthracene and 1 4-dimethyl-2.3-benzphenanthrene is 9 10-dimethyl 1.2-benzanthracene (XXIV) Both hydrocarbons are very active carcinogens.

Similarly chrysene is 1 2-benzphenanthrene and if methyl groups are introduced at positions 3 and 4 carcinogenic activity is obtained. Thus 3·4-dimethyl 1.2 benzphenanthrene is 1.2-dimethylchrysene (XXV) a moderately active carcinogen. 2 Methyl 3·4-benzphenanthrene (XXVI) is also moderately potent and it can be regarded as a phenanthrene derivative substituted at positions 2,3 4

Following this idea Hewett and Martin prepared 1 2 3 4-tetramethyl-phenanthrene (XXVII) and in line with the theory it was found to have slight, but definite, activity

The phenanthrene type double bond does seem to have some significance in the active compounds although it is clearly

CONTENTS

not the whole story. More recently some interesting correlations have been noted between carcinogenic activity and the electron density in this region of the molecule in benzanthracene derivatives.

Metabolism

The metabolism of the carcinogenic hydrocarbons has been widely studied in attempts to discover their fate in the body and if possible to obtain some insight into their mode of action. It had been observed that the carcinogenic hydrocarbon 1:2:5:6-dibenzanthracene was metabolised to different products in rats and in rabbits and it seemed possible that this difference in metabolism might be related to the fact that while 1:2:5:6-dibenzanthracene nearly always leads to tumour formation by subcutaneous injection in rats, it is practically inactive by this technique in rabbits. It has been found, however, that both carcinogenic and non-carcinogenic hydrocarbons appear to be metabolised by a similar route, and in all cases the hydrocarbons are converted into hydroxy derivatives.

Thus 1:2-benzanthracene is converted in rats into the 4-hydroxy compound (XXVIII). Chrysene is metabolised to 3-hydroxychrysene (XXIX) and 3:4-benzpyrene to the 8-hydroxy and 10-hydroxy derivatives (XXX). In rats and mice 1:2:5:6-dibenzanthracene gives the 4′:8′-dihydroxy derivative (XXXI) and the metabolite in rabbits has recently been identified as the 2′:6′-dihydroxy compound. It is interesting that in all these hydrocarbons metabolic oxidation takes place at comparable positions which are not the positions generally attacked in ordinary chemical reactions.

The hydroxy derivatives are in general non-carcinogenic, or only very weakly active, so that metabolism results in detoxification of the carcinogen. These and other results suggest that the metabolic pathway towards hydroxylation is not involved in the carcinogenic process, although we cannot be certain about this until more is known about the intermediate stages.

Using radio-actively labelled compounds Heidelberger has recently shown that aromatic hydrocarbons are firmly bound to skin protein and he has suggested that the induction of malignant change may be related to the gradual deletion of key proteins essential for the control of growth.

Biological properties

The biological properties of the carcinogenic hydrocarbons are very interesting. A characteristic feature of their action is that they act locally at the site of application. By application to the skin of experimental animals they cause first papillomas and then malignant tumours which have all the characteristics of carcinoma. They invade muscle and they give rise to secondary tumours usually in the lung or the axillary glands. If applied by subcutaneous injection they cause sarcomas which can be grafted and maintained in successive hosts apparently indefinitely. With these compounds tumours have been obtained in animals of several different species (mice, rats, fowls, guinea pigs and hamsters) and in a great variety of tissues. The tumours also show great variety morphologically and their nature seems to be determined mainly by the nature of the cells affected by the carcinogenic agent.

Differences between the compounds are quantitative rather than qualitative. Thus two compounds may differ in the rates at which their application to a given tissue leads to tumour formation but relative potencies found in this way may not be duplicated if a different test tissue is used.

Address of Welcome

Olof Soderstrom
President, Swedish Tobacco Monopoly

The sponsors of the symposium which is about to commence are the Medical Advisory Council of the Swedish Tobacco Monopoly and the Tobacco Research Committee of the Swedish Medical Research Council and it is my pleasure on behalf of these two institutions, to welcome all of you who are attending this symposium in the capacity of lecturers, members of discussion groups or interested listeners. I myself belong to the latter group and must admit to knowing relatively little about the subject and being perhaps not completely impartial. May I first extend my very sincere thanks to our guest lecturers who have taken the time and the trouble to travel to Stockholm and give us the benefit of their extensive knowledge and the results of the research work which they have carried out in the fields covered by this symposium. We feel certain that what they have to say will do much to stimulate the research work on the use of tobacco recently initiated in Sweden and we hope that we shall be able to extend the scope of our efforts in this sphere. For the benefit of those of you who may not know I would mention that our guest lecturers are the elite of their particular specialised field and this made us all the more happy when they accepted our invitation to attend. I would also extend a hearty welcome to our other guests from abroad—none mentioned by name but none forgotten—and to the delegates from certain Swedish authorities and research institutions whose activity is associated with the problems which we shall be examining during the course of the next two days. I also wish to welcome all the scientists who actively supported by the sponsors of this symposium, are engaged in investigations into the use of tobacco and its effects. I thank them for their part in contributing brief details of their particular work insofar as this is related to the subjects of the main lecturers. Naturally all other delegates are equally warmly welcome. Since this symposium is by invitation only I know that our guest lecturers have a very interested—and expert—audience. We have, may I mention, three Nobel Prize Winners present.

I should now like to say a few words about the part played by the sponsors in the field of research with which we are dealing. As I mentioned a few moments ago research in this field is comparatively new in Sweden, but this is perhaps not surprising. A small country must concentrate its research resources on the most urgent problems. Moreover the use of tobacco is on a smaller scale in Sweden than in most other countries. To quote an example, our consumption per adult inhabitant is only about 1/3 of that in the United States and Great Britain. In that consumption of tobacco in recent years

There may also be large differences in response in passing from one species to another for example it is much more difficult to produce skin tumours in rats with 3·4-benzpyrene than in mice and it has been reported from the United States that monkeys have been treated for 15 years with methylcholanthrene a very potent hydrocarbon carcinogen to mouse skin, without producing a single tumour

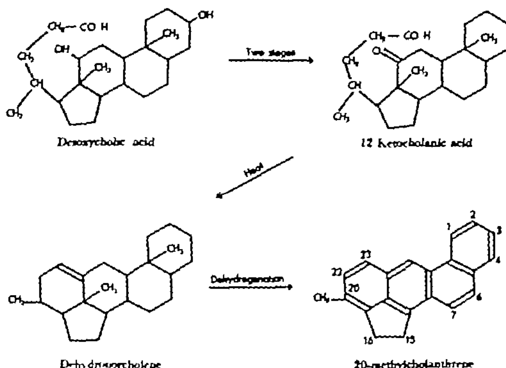
Nevertheless the certainty with which malignant tumours are produced, e.g by painting on mice with the more potent compounds is very impressive as also is the smallness of the dose, amounting in the case of the more active compounds to microgramme quantities, with which tumours have been produced.

Methylcholanthrene and Cholesterol

A particularly interesting carcinogen of the benzanthracene class is 20-methylcholanthrene which is, in fact, one of the most potent carcinogenic hydrocarbons known. This hydrocarbon has been prepared synthetically but even before that in 1933 it had been obtained independently in two laboratories in Germany and in the United Kingdom from desoxycholic acid, a normal constituent of human bile and its strong carcinogenic activity had been predicted by Cook.

It was later obtained also from cholic acid and from cholesterol

It is interesting to speculate whether cancer of the internal organs of man may not arise through the action of chemical carcinogens which may have been produced by some such abnormal metabolic pathway from steroid type compounds in the body There is no evidence to suggest that reactions of this type could or do take place in the body but equally there is no evidence that they could not and the possibility remains. If the high activity of



Desoxycholic acid

12 Ketocholanic acid

Dehydronorcholene

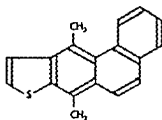
20-methylcholanthrene

Acting on the recommendation of its medical council the Monopoly has allocated considerable funds for research purposes. I should like to mention in this connection that all projects recommended by the council have been backed by the Monopoly to the extent recommended by the council. The Monopoly the Swedish Medical Research Council and the Cancer Society have also defrayed the cost of more expensive research measures.

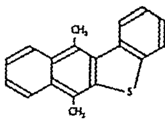
The collaboration practised between the Tobacco Research Committee of the Medical Research Council and the Monopoly's advisory council is also exemplified by the fact that these two institutions are the sponsors of this symposium. As will be seen from the programme the symposium will deal mainly with chemical and biological problems associated with smoking. It is the hope of the sponsors that it will be possibl at some later dat to hold symposia dealing with other aspects of tobacco research.

I should like to emphasize that the aims of the symposium are purely scientific. Its main aim is to provide an opportunity for Swedish researchers to gain knowledge of what foreign experts consider to be the major problems, the steps that have been taken to eliminate them and the progress recorded to-date. We also hope, of course that the symposium will encourage especially Swedish scientists to endeavours in this field and that, as a consequence, new research workers will engage themsel es in the solution of the important questions listed on the programme drawn up by the council. We are also convinced that the personal contacts established at a symposium of this kind will foster the interest in research.

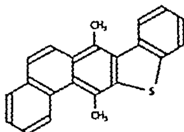
W th these words I once more wish you all a hearty welcome



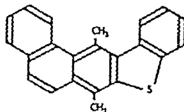
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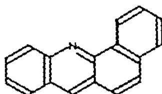
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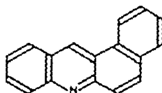
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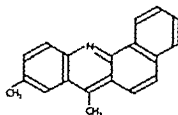
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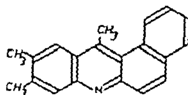
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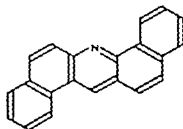
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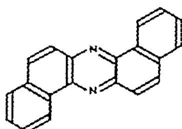
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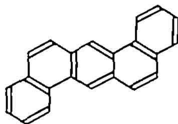


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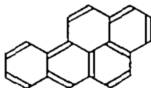
isoprene. It was concluded that the active constituents of these tars were probably polycyclic aromatic hydrocarbons and it was noted also that many of the most active tars exhibited an intense fluorescence, which was similar to that of 1.2-benzanthracene. Following up this clue a number of derivatives of 1.2-benzanthracene were prepared and tested in Kennaway's laboratory. Two of these 1.2 .5:6-dibenzanthracene (I) and 6-isopropyl-1.2-benzanthracene



I

cene were found to have quite strong cancer producing activity by skin painting experiments on mice.

The fluorescence of these substances was not identical with that of the active fractions of coal tar but soon afterwards another potent cancer producing substance was isolated from coal tar by Cook and Hieger and identified as the pentacyclic aromatic hydrocarbon 3·4-benzpyrene (II). This substance had the typical fluor



II

escence spectrum of coal tar and other carcinogenic tars. It was prepared synthetically in the laboratory and the biological properties of the synthetic material were identical with those of the material isolated from the tar. 3·4-benzpyrene is one of the most potent carcinogens known. It readily produces malignant tumours when painted on mouse skin and gives rise to sarcomas when applied by subcutaneous injection. More recent work has shown that coal tar contains other carcinogens besides benzpyrene. These other carcinogens have not yet been identified but it is probable that they also belong to the class of polycyclic aromatic hydrocarbons. Whether the carcinogenic activity of lubricating oils is also due to aromatic hydrocarbons is still an open question, but experiments in progress in our laboratory in Exeter indicate that they may be implicated here also.

Because of its widespread distribution the carcinogenic activity of 3·4-benzpyrene is of some practical importance. It is a fair presumption that it is responsible, at least in part, for the skin cancer in coal tar workers although direct proof would naturally be difficult to obtain. It has been obtained from carbon blacks and from at least one sample of a cracked mineral oil and has recently also been isolated from cigarette smoke by Wynder and Hoffman. All of these materials are carcinogenic to experimental animals and the 3·4-benzpyrene undoubtedly contributes to their activity. It has been identified also in domestic soot and in the exhaust gases of internal combustion engines and, inefficiently operating diesel engines and with other aromatic hydrocarbons, appears to be a product of incomplete combustion of organic material. It has also been found in the atmospheric dusts of cities. The following table, which is taken from data presented by Doll, shows the amounts of 3·4-benzpyrene found in the atmospheres of a number of cities in Britain and Scandinavia.

benzene containing amino or methylamino groups. The positions and nature of the substituent groups are of considerable importance for the activity.

The carcinogenic azo dyes are slow acting and large doses are required to produce tumours. In contrast to the aromatic hydrocarbons which give rise to local tumours at the site of application, the azo dyes have a specific action and produce, for the most part, only tumours of the liver irrespective of the route of administration, a fact which suggests that the true carcinogens are *not* the azo dyes themselves but some metabolic products produced in the liver. It is of interest in this connection that azo dyes have been found to be firmly bound in the livers of treated animals.

The action of the azo dyes in producing liver tumours is of some practical importance, for some compounds in this class have been used as food colouring matters, although it is unlikely that sufficiently large amounts could be ingested in this way to cause danger. Diet plays an important role in this type of carcinogenesis. Deficiency of protein and of riboflavin favours the production of liver tumours in rats, while with more balanced diets tumour formation is delayed or entirely prevented.

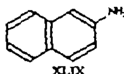
Aromatic Amines

Another class of carcinogens is formed by some aromatic amines. Among these β-naphthylamine (XLIX) is important, for it is undoubtedly one of the substances responsible for the occurrence of bladder cancer among workmen in the dyestuffs industry. The pure amine produces bladder tumours when fed to dogs, rats and rabbits over a prolonged period. The true carcinogen appears to be the metabolite 2-amino-1-naphthol (L). Conjugates of this compound were found in the urine of dogs treated with the amine and the free hydroxy compound gave bladder tumours when implanted in mice, although β-naphthylamine itself was inactive when tested by this technique.

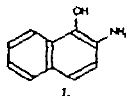
The evidence linking β-naphthylamine with bladder cancer is now so strong that production of this important dyestuff intermediate is no longer carried out in the United Kingdom.

Aromatic amines of other types are also carcinogenic, including some derivatives of diphenyl.

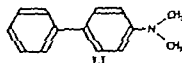
Dimethylaminodiphenyl (LI) has been shown to be a potent carcinogen in the rat when administered by subcutaneous injection, producing tumours in a variety



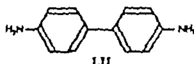
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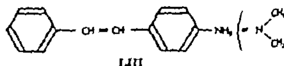
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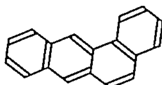
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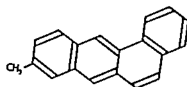
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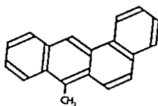
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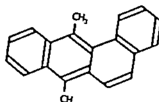
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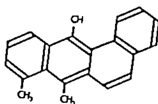
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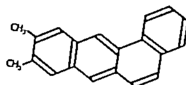
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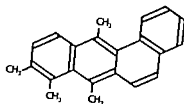
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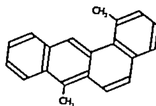
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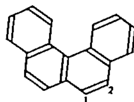
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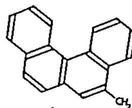
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XI



XII

arsenite and arsenious acid, and insecticides (copper or lead arsenite) A number of cases of medicinal arsenical cancer have been reported in patients treated with various inorganic arsenical drugs and there is evidence that arsenic may also be involved in the origin of some cases of human lung cancer A number of attempts have been made to produce cancer in laboratory animals by administration of arsenic but no satisfactory evidence of success has been obtained possibly because of its toxicity

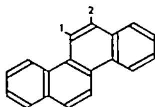
An increased incidence of lung cancer among some employees in the chromate industry has been attributed to inhalation of chromium salts but the exact chemical nature of the carcinogenic agent is still uncertain. Heuper has obtained sarcomas in rats, following implantation of chromite ore roast. Finely divided nickel and nickel carbonyl have been held responsible for the high incidence of nasal cancer and lung cancer among men working in factories operating the Mond Nickel process. Heuper has reported the production of a number of cancers in rats following injection of nickel powder in lanolin.

Osteogenic tumours have been obtained in rats following administration of beryllium and Vorwald has obtained lung tumours in rats after prolonged exposure to an atmosphere containing beryllium salts. Beryllium is retained in the human body for very long periods and produces curious histological changes in the lung but so far none of these has been shown to be cancerous.

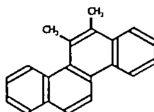
Mention should also be made of the astonishing results observed recently by Richmond and by Haddow They have obtained sarcomata in a large proportion of rats and mice treated by injection with massive doses of an iron-dextran complex widely used in medical practice in treatment of anemia. It is not yet known whether this result is due to the iron alone, or to the complex as a whole.

Remarkable results have also been obtained by Oppenheimer and others by implantation of films of a variety of synthetic plastics nylon, teflon, cellophane, polythene, etc. in rat tissue. After long latent periods sarcomata were produced in a considerable proportion of the animals treated. Similar results have also been obtained with silk fibres and Prof Druckrey has produced tumours in rats by implantation of asbestos fibre and asbestos powder It is difficult to conceive that a chemical mechanism is involved in these cases and indeed in the case of the synthetic plastics at any rate the physical state of the materials appears to have some effect on the carcinogenic response, for although films of plastic produced sarcomata, the powdered substances did not.

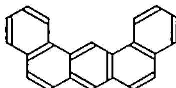
This by no means exhausts the list of agents which have been shown to have carcinogenic properties. In this brief and rather superficial survey I have tried to give you some indication of the diversity of chemical types which have been shown to be carcinogenic and of the variety of response they can evoke in experimental animals. In spite of a great deal of research we still know very little of the way in which these substances produce their effects. Their very diversity has complicated rather than simplified attempts to understand their action. It seems likely that they may act initially by different mechanisms, but much work remains to be done before we can measure their full significance.

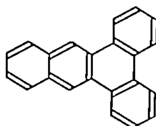


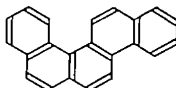
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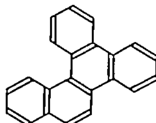


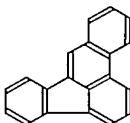
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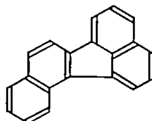

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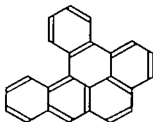

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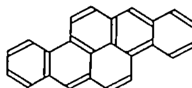

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Experimental Investigations on the possible Carcinogenic effects of Tobacco Smoking

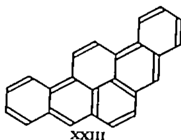
Professor Dr H. Druckrey
Freiburg Germany

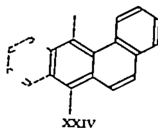
The possible cancer risk of tobacco smoking is a serious problem, not only to the medical profession and to scientific research but also to the manufacturers of tobacco products At the same time it is certainly a very difficult and complicated problem, which in my opinion needs a very close cooperation between scientists in different fields, as well as between health authorities and tobacco manufacturers of all interested countries. As a result of my experience in similar fields I am convinced that real progress will arise only by such cooperation with genuine mutual confidence. Being an optimist I think that, in principle, the technical problems can be eventually solved. At the present time however the possible risk of tobacco smoking should be considered purely as a scientific problem. That means, it should be investigated without any prejudice, without any bias, and completely uninfluenced by commercial viewpoints. If the problem is discussed in such a way and in full confidence between research workers and industrial investigators, then I think a symposium like this may be very helpful for future development. I very much appreciate the fact that the Swedish Tobacco Monopoly organized this symposium and I am very happy to participate in it.

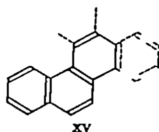
When considering the possible cancer risk of tobacco smoking we have to deal in the main with two groups of problems 1) the chemistry and physical chemistry of the suspected materials and the processes involved 2) the medical aspects, especially pharmacology and pathology Being a pharmacologist I want to restrict myself to my own field.

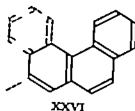
As far we can say at the moment, the mechanism of carcinogenesis is in some respects different from what we know of the mechanism of other drugs. Many special problems are involved which must be investigated thoroughly In order to form a proper pharmacological assessment the first question would concern the nature of the active substance or substances and the specificity of its possible carcinogenic action the second would concern the nature of the dose-response relationship. This includes the problem of the efficacy of small doses and the existence of a threshold dose, which can be considered as "safe The final problem is that of the reversibility or irreversibility of carcinogenic effects and the time factor involved.

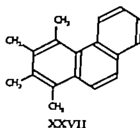
It is the wisest course in pharmacology to start an investigation with quantitative aspects in mind, so as to lay a proper basis. Since such quantitative experiments are very difficult with tobacco products and


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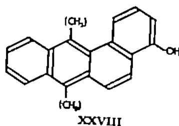

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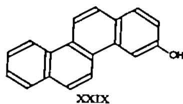

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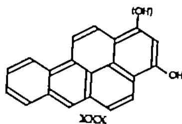
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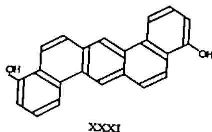
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XXX



XXXI

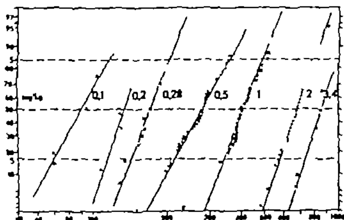


Figure 1 Incid nc | ear-duct arcinomas i dependenc on the total dose | 4-DASt for 7 separat dosng s anging from 0.1 to 3 4 mg/kg per d y F d ing periment in BD II rat continou t atment p to tu mou ppearanc Dots esp crosses ats with carcinoma. Or dinate Probits Percentag s f carcinomas Abscissa 5 times elongated.

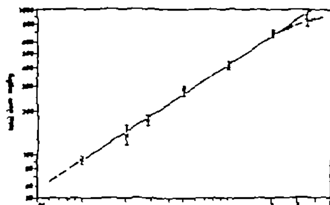


Fig 2 Linear d pendenc of the arcinogenic total dose (Dw) on th daily dosag of 4-DASt F ding experiments BD II ats conti uou t atme t Rang 3 standard deviation of the m dium values f th total dose (P=0.01) O d at total dose dministered p to tumour ppearance i 50 per ent f at Abscissa daily dosag in mg/kg body weight.

hardly detectable in the diet of the rats by chemical means. Since the induction time in this dosage group was 900 days and is therefore of the same order as the maximum lifespan of rats, we can conclude definitely that the effects of all successive doses, even the smallest, remains completely irreversible over the whole lifespan, and these effects sum up until finally the manifestation of a carcinoma occurs.

The medium values for the total doses (D_{50}) and the induction times (t_{50}) observed in the different dosage groups are summarized in Table 2. They show that with the highest daily dosage of 3 4 mg/kg the total dose for the production of cancer in 50 per cent of the rats was 850 mg kg against only 90 mg/kg with the smallest dosage of 0 1 mg/day the difference being nearly tenfold.

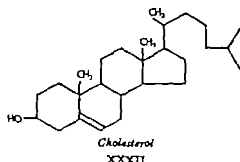
d daily dosage mg/kg	t ind ctio time days	D_{50} total dosage mg/kg
3 4	250	85?
2.0	342	685
1.0	407	407
0.5	560	280
0.28	607	170
0.2	675	135
0 1	900	90

Table Dose-response relationship in the production f ar-duct arcinomas by 4-DASt. F d ing periment in BD II at

this substance to mouse skin were duplicated in human tissues then, of course only very minute amounts would be necessary to induce cancer It is important to realise that if chemical compounds are concerned in the initiation of human cancer in general, their effects may be brought about by very small amounts of highly active compounds or by larger amounts of weaker carcinogens acting over a longer period perhaps the major portion of the life span.

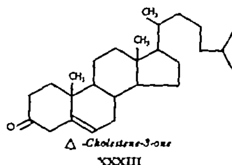
In this connection it is interesting that Hieger and others have obtained sarcomas in a small proportion of mice treated by injection with non-saponifiable fractions obtained from livers of people who had died, not only of cancer but also of other diseases. The main constituent of these fractions is the normal body constituent cholesterol and small yields of sarcomas have also been obtained in mice by subcutaneous injection of cholesterol specimens of varying degrees of purity and also of some oxidation products of cholesterol.

Fieser has pointed out, however that since the total amount of cholesterol (XXXII) in a man weighing 65 kg is



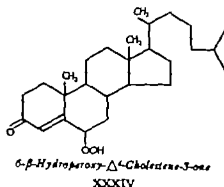
Cholesterol
XXXII

approximately 210 g it might seem unlikely that it is the true carcinogen he considers that its apparent activity must be due to some transformation product. He obtained tumours in 13 of 32 mice by injection with the hydroperoxide shown which was readily obtained by air oxidation of Δ^4-cholesten-3-one (XXXIII)



Δ -*Cholestene-3-one*
XXXIII

There is some indirect evidence that the Δ^4-cholestene 3-one can be formed in the body from cholesterol. Hieger maintains, however that cholesterol is itself carcinogenic. He has been unable to confirm the high activity of the hydroper



6-β-Hydroperoxy-Δ^4-Cholestene-3-one
XXXIV

oxide (XXXIV) We must leave these interesting speculations, however and return to the chemical carcinogens.

Heterocyclic Carcinogens

Carcinogenic activity has been found in a number of heterocyclic compounds related to the aromatic hydrocarbons.

The thiophen derivative 4-9-dimethyl 5-6-benzthiophanthrene (XXXV) which is related to 9 10-dimethyl-1.2-benzanthracene, is a very potent carcinogen and produced tumours in mice after a latent

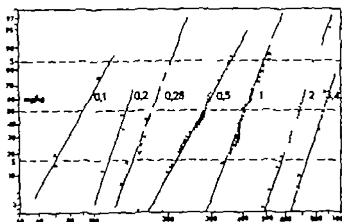


Figure 1 Incidence of ear-duct carcinomas in dependence on the total dose of 4-DASt for 7 separate dosages ranging from 0.1 to 3.4 mg/kg per day. Feeding experiment in BD II rats continuous treatment up to tumour appearance. Dots resp. crosses rats with carcinoma. Ordinate: Probits, Percentage of carcinomas. Abscissa: 5 times dosages d

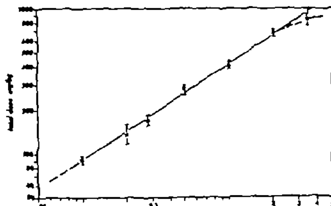


Figure 2 Linear dependence of the carcinogenic total dose (D_{50}) on the daily dosage of 4-DASt. Feeding experiments in BD II rats, continuous treatment. Ranges: 3 standard deviations of the medium values of the total doses (P = 0.01). Ordinate: total doses administered up to tumour appearance in 50 per cent of rats. Abscissa: daily dosages in mg/kg body weight

hardly detectable in the diet of the rats by chemical means. Since the induction time in this dosage group was 900 days and is therefore of the same order as the maximum lifespan of rats, we can conclude definitely that the effects of all successive doses, even the smallest, remains completely irreversible over the whole lifespan, and these effects sum up until finally the manifestation of a carcinoma occurs.

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Table 2 Dose-response relationship in the production of ear-duct carcinomas by 4-DASt. Feeding experiment in BD II rats.

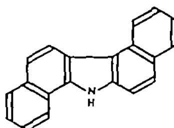
period of only 116 days. The isomeric compound 4 7-dimethyl-2.3 .5:6-dibenz thianaphthene (XXXVI) was only slightly active to skin, however and inactive by injection. This has been attributed to the fact that this compound no longer possesses a phenanthrene type double bond. Activity of a high order returned in the two benz-analogues (XXXVII) and (XXXVIII)

Among nitrogen heterocycles particular attention has been devoted to 1.2 and 3:4-benzacridine (XXXIX and XL)

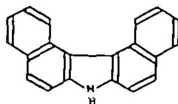
1.2 Benzacridine is itself inactive but derivatives with methyl groups in certain positions show activity of a high order Thus 5 7 (XLI) and 5:8-dimethyl- 1:2 benzacridine are very potent skin carcinogens. Derivatives of 3·4 benzacridine are not quite so active thus the trimethyl compound shown (XLII) is only a moderately active carcinogen.

In the pentacyclic series 1.2 .5·6-dibenzacridine (XLIII) is carcinogenic, but strangely 1:2 .5·6-dibenzphenazine (XLIV) is inactive, another example of how a small variation in the structure of a carcinogen can lead to loss of activity

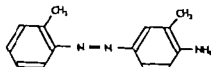
Both 1:2 :5·6- (XLV) and 3·4 :5·6-dibenzcarbazole (XLVI) in which we have a 5-membered nitrogen ring are active, but they differ from the compounds which have just been discussed in that they produce tumours in the liver in addition to local tumours at the site of application.



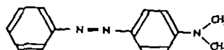
XLV



XLVI



XLVII



XLVIII

Azo Dyes

An entirely different group of nitrogen containing chemical carcinogens are the azo dyes. These are compounds containing the grouping -N=N linked to particular types of aromatic nuclei they are synthetic compounds and all are highly coloured. The first carcinogenic azo dye was discovered by Yoshida in Japan in 1933 He obtained hepatomas in rats by administration of o-aminoazotoluene (XLVII) with their food.

Soon afterwards Kinosita reported that the isomeric 4-dimethylaminoazobenzene (XLVIII) was even more active in producing liver tumours in rats. This substance was formerly used as a food colouring matter under the name of "butter yellow"

A large number of other azo compounds has since been prepared and tested and many have been found to be potent liver carcinogens. Nearly all the active compounds of this class are derivatives of azo-

gure 3 shows, that the tumour yield is nearly constant at 100 per cent up to medium age and only the length of the induction time increases with decreasing dosage. But the more the normal death rate interferes, the more the percentage of tumours decreases until finally it becomes zero, apparently because the expected induction time becomes longer than the maximum lifespan. Strikingly similar results have been observed by H. F Blum (6) in the production of cancer by ultra violet light.

From this it follows that when dealing with weak carcinogens or small dosages each increase of the lifespan should produce a corresponding increase in the frequency of cancer Figure 4 shows schematically how a prolongation of the lifespan would lead to a higher frequency of cancer for two different conditions (from point A to B or point C to D) This corresponds very clearly to practical experience with human cancer

To investigate this experimentally we tried systematically to prolonge the life span of our rats by increased care It was possible to reach a medium life span (50 per cent survivors) of 930 days against 550 days in former years. Only under these conditions could the carcinogenic action of small dosages, such as 0 1 mg 4 DASt, be demonstrated clearly which was not feasible before. From this the great importance of the time factor in carcinogenesis can be clearly seen.

In this respect the possible risk of discontinued exposure to a carcinogen is of special interest and this was also investigated experimentally Rats of our BD III inbred strain have been treated with 4 DAB in the diet, the daily dosage being a constant 5 mg per rat. After administration of a predetermined total dose, ranging from 1000 down to 200 mg the treatment was stopped but the observation of the rats continued until normal death. The results of these experiments were as follows. The smaller the total dose was, the longer was the induction time but on the other hand the tumour yield decreased considerably from 81 per cent in the group with the highest dosage of 1 000 mg per rat to only 20 per cent with 200 mg On plotting the percentages of tumour yield on a probit scale against the total dose administered using a log dose abscissa a linear relationship resulted (Figure 5) corresponding to the observations

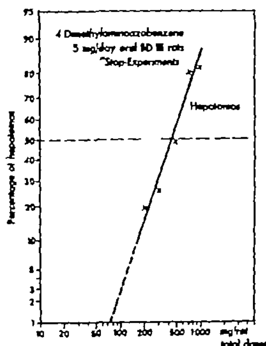


Figure 5 Incidence of liver cancer in rats dependent on the total dose of 4-DAB administered by discontinued doses The treatment was interrupted after total dose of 200 300 500 700 and 1000 mg 4-DAB respectively

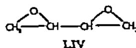
mentioned before (Figure 1) Therefore an extrapolation to the possible risk of smaller doses is valid. This of course can only be calculated in terms of probability in line with pharmacological

of urea. Benzidine (LII) has been proved to be a bladder carcinogen for man. It produces bladder tumours in dogs.

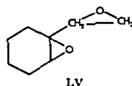
Aminostilbene (LIII) and several substitution products produced tumours in a variety of organs in the rat when administered subcutaneously or by mouth.

Biological Alkylating Agents

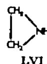
Other types of compounds which have been shown to be carcinogenic are certain



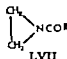
LIV



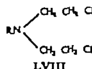
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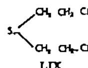
LVI



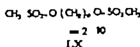
LVII



LVIII



LIX



LX

di-epoxides, e.g. the di-epoxide of butadiene (LIV) and of vinylcyclohexene (LV) some ethyleneimines (LVI—LVII) and the nitrogen and sulphur mustards (LVIII–LIX). Related to these is the recently discovered group of dimethane sulphonoxyalkanes (LX). These are all inactive to skin but they produce tumours by subcutaneous injection, mainly in the lung.

In contrast to the polycyclic hydrocarbons these substances are all highly reactive and they act as cytotoxic agents. They appear to react directly on the chromosome mechanism of the cell and in so doing bring about effects very similar to those produced by X-rays, which are also carcinogenic.

Recently Kotin and Falk have obtained skin tumours in mice and rats by application of a number of pure epoxides, and of synthetic mixtures consisting chiefly of oxidation products of aliphatic hydrocarbons derived from gasoline. By inhalation of these mixtures, which are thought to contain epoxides, lung tumours were produced in mice, and these authors are of the opinion that contamination of the atmosphere with products of this type may be at least partly responsible for the excess lung cancer incidence which has been noted among dwellers in certain cities in the United States.

Inorganic Carcinogens.

Finally I would like to refer briefly to a number of inorganic carcinogens which may be of importance in cancer of occupational or environmental origin. The role of arsenic in the production of skin cancer in men in certain occupations is now well established. Cases have been noted among employees in factories manufacturing sheep dip preparations containing sodium

am aware that a great amount of investigation still has to be done before any definite conclusions can be drawn. For such reasons we preferred not to publish the results of our experiments, which have been systematically in progress since 1952. My coworkers are Dr D Schmähl and H. Beuthner

In our experiments rats were purposely used. Firstly because nearly all experiments until now especially the basic work of Dr E. Wynder (8) have been done with mice and it seemed to be useful to have experiments with another species. Moreover with mice skin the special problem of cocarcinogenic factors is included which, as far as we know does not apply to rats. The second reason was that in the field of cancer production we have experience with our rats for more than 25 years and we can employ 10 different inbred strains, developed in the last 25 years. All of these have been used so as to avoid special results which may be obtained with a special strain.

The administration of the carcinogen was always done by subcutaneous injection. This has the advantage of an accurate dosage. The main reason however was, that with this technique local as well as systemic effects can be observed, whilst skin painting is limited mainly to such carcinogens as can be detected from their local action. Finally according to our experience, the subcutaneous tissue of rats is sensitive enough to show the effects even of weak carcinogens or small doses.

In 1954 a close cooperation with German tobacco scientists was initiated. In the first groups of experiments we used cigarette smoke condensates which had been prepared in their laboratories. These condensates were produced by a standard smoking machine and collected by the electrostatic as well as the cold trap methods. Nicotine was extracted with dilute hydrochloric acid and the benzpyrene content was determined by Dr Grimmer at the Institute of Organic Chemistry in Hamburg

Subcutaneous injection was done with a dosage of 55 mg per rat, once a week, the condensate being in 33 per cent solution in a mixture of tricaprylin and alcohol All solvents were carefully checked with ultraviolet light in order to make absolutely sure that no impurities of higher aromatic hydrocarbons were present. The control group was treated with injections of the solvent, i.e. the mixture of tricaprylin and alcohol, in the same dosage as was given to the experimental groups.

After having administered a total dose of 3.2 g of the smoke condensates, corresponding to 58 weeks, the treatment was stopped. The reason for the use of this "stop technique" was that, according to our pharmacological experience, the unspecific toxic effects are commonly reversible within a few days whilst the carcinogenic action is principally irreversible and progresses even after discontinued treatment. Therefore after the interruption of the applications the unspecific effects or lesions will disappear with time, so that the development of tumours weeks or months later gives better indication for a real carcinogenic action. The observation time however was extended over the whole lifespan, which we tried to prolong as much as possible by proper care of the rats. After natural death each rat was dissected carefully For the histological diagnosis we are indebted to Professor H. Hamperl, pathologist in Bonn.

In comparative experiments two different types of cigarette smoke condensates have been used, called A and B. The A-type was from cigarettes produced in the normal way and in the production of the type B an attempt was made to make the combustion process in smoking as

DISCUSSION

D Eh enb g Just ery short question. Has the ethyleneimine or some simple ethyl derivative of it been proved to be carcinogenic so far?

Dr Carruther Yes, by injection. Ethyleneimine itself and range of ethyl derivatives are report ed to have produced lung tumours by jection.

Prof Klein May I ask Dr Carruthers two brief questions, one being rathe theoretical and the other more practical. — I wonder if you would care to comment th theory put forward by French theoretical chemists on relationship between electron density in certain regions of the molecule and carcinogenic activity of aromatic hydrocarbons This was my theoretical question and my practical one would be th following You have mentioned, I think in connection with some aniline dye, that its produc tion is now prohibited in Great Britain because the evidence that t is carcinogenic is overwhelming I think it would be interesting for several of us to hear what is the policy in this respect in Great Britain. Just what evidence is required before you decid to prohibit the use of compound?

D Carruthers. I cannot say what the policy is. It is thought by manufacturers that the evidence linking β-naphtylamine to bladder cancer is now so strong that they feel disposed to prohibit its manufacture. But whether this is obligatory or not I don t know —As far as the theoretical point is concerned, French theoretical physicists try to relate the carcinogenic activity of aromatic hydrocarbons, particularly benzanthracene derivatives to the elec tron density in th phenanthrene-type double bond. They obtain theoretical results in which th electron density in the most active hydrocar bons of this type appear to lie within certain region. Inactive compounds are either above or below the prescribed limits of electron density Eventually chemical methods were obtained for measuring the electron density in this region and some correlation was noted experimentally Some confirmation was obtained experimentally for the theoretical results. But there are some exceptions and the French school now seems to think that their first idea was perhaps too simple and perhaps the electron density in other regions of the molecule may also be important.

span, two years after the beginning of the exposure. This corresponds to 50 to 60 years for human beings. Therefore, as far as results from animal experimentation can be applied to human conditions, the *medium* exposure time or induction time for heavy smokers to develop lung cancer may be longer than 30 years as generally assumed but should be expected to be of the order of 60 years or even more. This means that the manifestation of bronchogenic cancer occurs only in the most sensitive persons and therefore in a limited number of heavy smokers whilst the greater part does not survive long enough for tumour development. This corresponds very well to experimental results given in the first part of this paper and is certainly not a mystery at all. But it leads necessarily to the very important practical conclusion, that young people must be warned especially at least not to start smoking too early In principle the cancer risk is greater the younger a person is at the beginning of exposure to tobacco smoke. Therefore the protection of the youth from any carcinogenic risk must be considered as fundamental for practical cancer prevention (9) This applies also to pregnants.

A further indication that smoke condensates are only weak carcinogens follows from the fact that the subcutaneous tissue of rats is relatively sensitive to locally acting carcinogens and that the tumour growth was slow However the production of local sarcomas at the site of injection in these experiments cannot be considered as a nonspecific effect since practically no tumours have been observed in the control rats treated with the pure solvent at the same dosage schedule. According to our long experience this subcutaneous injection technique in rats proved to be most useful in testing substances for local carcinogenic properties The subcutaneous tissue of rats is apparently more sensitive than even the skin of mice. This is especially important for the investigation of carcinogens as weak as tobacco smoke condensates.

Now the fundamental problem of the chemical nature of the carcinogenic material in tobacco smoke condensates appears. At the present time the higher aromatic hydrocarbons are blamed mainly 3·4-benzpyrene, since it is one of the most potent carcinogens, and its presence in tobacco tar has been demonstrated conclusively by many investigators But on account of the very low concentration of only 1 mg benzpyrene per kg smoke condensate there remains some doubt as to its decisive importance Since every prejudice in this field may be misleading, we considered it as necessary to perform comparative experiments with solutions of pure 3·4-benzpyrene.

For this purpose two experiments have been started One group of 47 rats was treated with subcutaneous injections of crystalline 3·4-benzpyrene dissolved in a mixture of pure tricaprylin and alcohol at a dosage of 1 microgram once per week over the whole lifetime. In a second group of 46 rats a mixture of 1 μg of benzpyrene and 10 μg each of pyrene and anthracene per dose was used. For control 50 rats were injected with the pure solvent. The results are presented in Table 3 With benzpyrene 1 abdominal sarcoma and 1 lymphosarcoma was observed but this only after 1 year of treatment, whilst the rats surviving longer remained without tumour Since these types of tumours occasionally occur "spontaneously" in our rats and have been observed in the control group with at least the same frequency no causative relationship to the benzpyrene treatment can be assumed. Only in the second group treated with the mixture of the three hydrocarbons, one

have not been feasible until now I want to mention a few quantitative experiments we made with other carcinogenic substances in order to provide a definite basis for the discussion here about the type of risk which may be involved with tobacco smoking

Our first quantitative experiments (1) were carried out with 4-dimethylaminoazobenzene (4 DAB, "butter yellow") This substance produces liver cancer in feeding experiments with rats after chronic exposure The results of these quantitative tests are summarized in Table 1

d daily dosage mg	t induction time days	D total dose mg
30	34	1020
20	52	1040
10	95	950
5	190	950
3	350	1050
1	700	700

Table 1 Dose-response relationships in the production of hepatomas by 4-DAB Feeding experiments in BD III rats continuous treatment

They show approximately an inverse proportionality between the length of the induction time and the daily dosage. The total dose administered until the appearence of the tumour is nearly the same in all groups and is not increased by fractionation. From this it follows that the production of the liver cancer is a function of the total dose, even if its administration includes the whole life span. This means, that the effects of all successive doses remain completely irreversible over the whole life span and integrate with time. Therefore we proposed for this new type of pharmacological action the term "summation action" It is defined as a function of the sum of all successive doses (2)

According to pharmacological experience the risk of a poison by chronic exposure depends upon the reversibility of the effects (3) The lesser and slower the reversibility is, the more the effects accumulate up to a summative effect. Since the effects of carcinogens, as will be demonstrated later are apparently irreversible, such substances must be considered as especially dangerous.

The reproducibility of the results observed in the experiments with 4-DAB had to be tested with other carcinogens producing other types of cancer We used the 4-dimethylamino-stilben (4-DASt) which, according to Haddow Harris, Kon and Roe (4) produces ear-duct carcinomas by oral administration in rats. The quantitative experiments have been performed with my coworkers D Schmähl and W Dischler in a similar way as before with 4 DAB. Seven dosage groups were used with constant daily dosages of 4-DASt, namely 3 4 2.1 0.5 0.28 0.2 and 0.1 mg/kg body weight. This treatment was continued until the first appearance of a tumour The total dose administered up to this time was then noted for each rat. The point is that, if the carcinogenic action is really a function of the sum of all successive doses, i.e. of the total dose, then a clear relationship between tumour appearance and the total dose must be expected.

The results were as follows. On plotting the appearance of each malignant tumour on a probit grid which has the percentage of carcinomas on the ordinate and the log of the total dose on the abscissa a clear linear relationship in all different dosage groups was obtained as is shown in Figure 1 (5) This figure demonstrates already that the total dose necessary for producing carcinomas in the different groups is smaller the lower the daily dosages that have been used, and this holds down to the very small dosage of 0 1 mg/kg per day This dosage is so small, that it is

tion of similar effects on subcutaneous tissue, especially in rats. Since moreover in this species only 1 per cent of the observed carcinogenicity of smoke condensates can be attributed to the benzpyrene content, it seems reasonable to look for other carcinogens rather than to discuss the possibility that 99 per cent of the action should be due to cocarcinogens. For such assumptions no sound scientific background exists, which it is indispensable to have. On the other hand the carcinogenicity of tobacco smoke condensates is now established beyound any reasonable doubt experimentally in mice as well as in rabbits and rats, it seems imperative therefore to look for other carcinogens without any bias.

The first problem to be considered is whether or not carcinogenic substances are preexistent in nonsmoked tobacco With tobacco extracts prepared with methanol and afterwards with methylene chloride E. Wynder and G Wright (11) obtained papillomas and carcinomas in mice using the skin painting technique. The tumour yield, however was considerably lower than with smoke condensates. This may be due to the solvent used. On the other hand there exist some statistical indications for a causative role of genuine tobacco in human cancers. V R. Khanolkar and coworkers (13) reported, that cancer of the mouth cavity the incidence of which is outstandingly high in India, representing about 50 per cent of all cancers in men, is observed mainly in people who chew tobacco. Therefore the possible presence of carcinogenic substances in tobacco leaves was discussed Furthermore R. L. Cooper and J M Campbell (14) directed attention to the high frequency of cancer in the nasal and sinus cavities in Bantu negroes who have the habit of taking tobacco snuff but smoke cigarettes only to a small extent. These experiments gave further impetus to investigate nonsmoked tobacco for carcinogenic activity

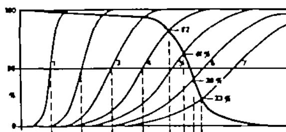
For this purpose 70 per cent alcoholic extracts of tobacco, as used for cigarettes, were prepared After extraction the alcohol was removed by vacuum distillation at low temperature. Employing this procedure 1 kg of tobacco yielded about 200 g of extract. Therefore the relationship "extract to original tobacco is 20 to 100 against the 2 to 100 for tobacco smoke condensate. The nicotine content of the extract was 1,5 per cent on the average. No benzpyrene was detectable For practical application in rat experiments the extract was diluted with a mixture of equal parts of glycerol and 70 per cent alcohol to a final concentration of 33 per cent. Control experiments with pure glycerol as well as with distillation residues of glycerol injected subcutaneously in rats showed no carcinogenic activity

This solution of tobacco extract was used for subcutaneous injection in the same strains of rats and following the same dosage schedule as was used in the former experiments with smoke condensates each dose being 57 mg referred to the original extract. The injections were continued once per week for a time of 465 days up to a total dose of 3.2 g per rat, the same amount as was used in the former experiments with smoke condensates Then the injections were stopped.

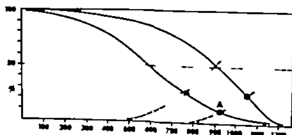
The number of rats injected with tobacco extract was 75 After each injection the rats showed convulsions lasting for a few minutes, due to the nicotine content of the extract. But the animals recovered very quickly The vitality was not depressed, the medium lifespan was about 800 days and therefore certainly not reduced as compared with the control rats. Four hundred days after the beginning of the injections a considerable number of rats developed tumours, nearly all of them sar

Plotting the results of table 2 on log log coordinates yielded a strikingly linear rela tionship between the carcinogenic total dose and the daily dosage. (Figure 2.) The first conclusion from this is, that the production of cancer shows a clear and surprisingly simple dose-response relation ship and does not need any metaphysical assumptions. On the other hand the results show that tumours can be produced by con tinous exposure, even with such a very small dosage as 0 1 mg/kg per day but this only after a very long induction time of 900 days. Since the rats at the begin- ning of exposure were already 100 days old, the tumours developed at an age of 1000 days, which is the maximum of life span of rats. Therefore the use of smaller dosages was not feasible because the in duction time would then become longer under such circumstances, than the life span. The linear relationship in figure 2 shows conclusively that an extrapolation to threshold dosages, which can be con sidered as "saf on continuous exposure is not possible. All my endeavours to find an indication of such a safe dose with carcinogens have been fruitless. The im- possibility of giving a fair estimate for any safe dose with carcinogenic substances is a very serious problem. On the basis of our experimental results the limiting fac tor in the production of cancer is appa rently the limited lifespan.

For such reasons the way in which the normal death rate may interfere with the production of cancer must be investigated. Such an interference naturally has to be respected the longer the induction time becomes in the case of small doses of po- tent carcinogens or of chronic exposure to weak carcinogens. These possibilities are demonstrated schematically in Figure 3 which is based on experimental results with 4 DAB carcinogenesis in rats. In this figure the variation of the percentage of tumour appearance with induction time, or age of the animals, is given by a number of sigmoid curves, each representing the action of a certain dosage The curve for the normal death rat goes inversely with age from 100 per cent down to zero. Fi



Figu 3 Th d pendenc of th length of th induction time and of the tumour yield pon th dosage for seven dosage groups (thin curve) and th interferen of th normal death rate (thick curve) O dinate Per- entag f tumou esp f su vivors. Abscissa time (H Druckrey Acta Unio internat Cancer 10 79 (1954)



Figur 4 Scheme for the increase of cancer incidence with prolongation of th lif pan.

per rat, corresponds to only 16 cigarettes against 160 cigarettes with the smoke condensate. It follows that the carcinogenicity of the tobacco extract seems to be considerably and perhaps ten times, higher than that of the smoke condensates.

The positive outcome of this experiment is so clear that no doubt seems to be possible. But in view of the practical consequences this experiment should be duplicated to make sure whether or not carcinogenic substances are really present in the tobacco itself If so the main problem is what chemical nature these substances might have.

A contamination of tobacco leaves by higher aromatic hydrocarbons, resulting from air pollution or from the drying process may be conceivable but the possible amounts are far too low to explain the observed carcinogenic effect (15) More attention should be given to the alkaloids and to the arsenic content. Since it is known that one cigarette produces only 0 01 microgram of benzpyrene but often contains 30 μg of arsenic and about 20 mg of alkaloids it seems somewhat premature to concentrate the investigations on hydrocarbons only and to neglect other possibilities. Since arsenic is carcinogenic to man I feel obliged myself to recommended as a practical contribution to cancer prevention, even if it is not the decisive carcinogen in tobacco, that in the production of tobacco no arsenical insecticides should be permitted.

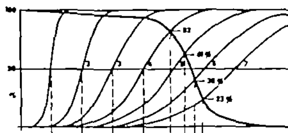
The strikingly positive results obtained with extracts of nonsmoked tobacco indicate that perhaps the greater part of carcinogens is preexistent in the tobacco and not produced by the process of smoking or pyrolysis. The same would apply to cocarcinogens if they play a role at all. Therefore the smoking should be considered, not only as toxicating process but rather also a detoxification of preformed carcinogens. This seems to be convincing to every chemist. For instance it is well known that even in the group of higher aromatic hydrocarbons, the most potent carcinogens are especially sensitive to oxidation, so that the detoxification may be enhanced if a more complete combustion is achievable. This of course has some bearing also upon the interesting assumption that the free radicals (16) developed in the combustion process may be one of the agents responsible for the carcinogenic action of tobacco smoke. At least it seems worthwhile to investigate the tobacco itself for carcinogenic activity without prejudice in order to provide a proper and sound basis for the problem of tobacco smoking and its cancer risk.

However even if the real nature of the causative agents cannot be established at the moment, the apparent carcinogenic risk of tobacco smoking demands preventive measures. This even more so because it is certainly not the only carcinogen to which human beings are exposed on a large scale, but only one of many These facts increase the responsibility of both scientists and manufacturers of tobacco products.

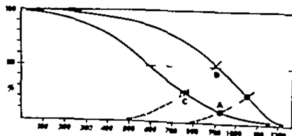
For a proper assessment of the possible risk the problem of dose response relationships must be considered as fundamental This was the reason that led me to present the quantitative aspects of carcinogenesis at the beginning of my paper In this respect I may mention some experiments we made some 6 or 7 years ago studying the fluorescence of cigarette smoke as an indicator of the absorption due to different types of smoking (17) The method was as follows one puff of cigarette smoke was blown into a washing bottle filled with pure nonfluorescent benzene. Then the bottle was shaken for complete absorption of the smoke and the fluorescence inten

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F gur 4 S heme for th increase of ancer incidence with prolo gation of the lif pan.

tance of the time factor in carcinogenesis is well known. All that we should have in mind is to serve human health and to contribute as much as possible to practical and useful means of cancer prevention.

SUMMARY

1) Quantitative aspects of carcinogenesis especially dose response relationships are presented as a basis for the assessment of the possible risk of environmental carcinogens.

2) Two types of condensed cigarette smoke have been tested for carcinogenic activity by subcutaneous injections in rats of different BD-strains. At a dosage of 55 mg injected once per week for a period of 60 weeks up to a total dose of 3.2 g condensate, corresponding to 160 cigarettes per rat, 28 out of 150 rats (19 per cent) developed malignant tumours, mostly at the site of the injections.

3) Control experiments with the pure solvent (tricaprylin, alcohol) gave completely negative results.

4) These results confirm the carcinogenicity of tobacco smoke as observed before on the skin of mice and rabbits, also on the subcutaneous tissue of rats. Considering however the relatively high dosage used, the low tumour incidence and the length of the induction time observed the carcinogenic activity is apparently only weak.

5) The repetition of the experiments in rats of the first filial generation gave the same result with condensate A, but a strikingly lower tumour incidence with condensate B, probably due to a more complete combustion. No indication is found for a transmission of the carcinogenic effects to the progeny.

6) Solutions of pure 3·4 benzpyrene or of a mixture of benzpyrene, pyrene and anthracene, injected at a total dose of 116 micrograms of benzpyrene produced practically no tumours as compared with controls. Since the benzpyrene content in 3.2 g of tobacco smoke condensate as used in the experiments is less than 3 micrograms, it can account for only about 1 or 2 per cent of the carcinogenicity of the smoke condensate. Therefore it seems necessary to look for other carcinogens without prejudice.

7) A 70 per cent alcoholic extract of unsmoked cigarette tobacco injected subcutaneously in rats of the same BD-strains following the same schedule has produced malignant tumours in 15 out of 56 rats up to the present, mostly at the site of injection. Four more tumours are still growing. The total dose of 3.2 g extract administered corresponds to only 16 cigarettes against 160 cigarettes with the smoke condensate. This suggests that the carcinogenicity may be inherent in the tobacco itself and that the smoking process should be considered as a detoxification rather than a toxicating process.

8) The positive outcome of the experiments with tobacco extract is not consistent with the view that cocarcinogens possibly produced in the smoking process, play an essential role in the carcinogenicity of tobacco products. This even more so since such cocarcinogenic effects, although well established on the skin of mice and rabbits, have not been observed for the subcutaneous tissue of rats.

9) Possibilities of practical cancer prevention are discussed.

experience. From the *results in figure 5* it can be concluded, that below a certain dose the probability of cancer manifestation becomes so low that it can be neglected. This indicates the existence of a threshold dose. But two things have to be borne in mind. The threshold dose concerns 1) only the total dose, i.e. the sum of all successive doses administered, and 2) the manifestation of cancer. When considering the carcinogenic effects of successive doses, however no threshold doses can be demonstrated as shown before. Furthermore we have to distinguish between the circumstances of animal experimentation and those in the human situation. In animal experimentation dose-response relationships can only be investigated properly down to about 5 per cent probability at the lowest. For lower percentages one would need hecatombs of animals, which is not feasible and I would not like to take the responsibility for doing this. When, however linear dose response relationships exist then extrapolation to lower probabilities is permissible. For human beings, however the assessment is necessarily completely different. A probability of a few percent, which means nearly nothing in animal experimentation and cannot be proved in a quantitative way means, in contrast, a lot of human beings considering the hundreds of millions of people which may be exposed to certain carcinogens. Therefore we have to extrapolate the dose response curves to probabilities in the order of 1 10 000 to give sufficient safety and to be able to guarantee noncarcinogenic activity (3). This is an aspect of highest practical importance. But the striking point I want to stress once more is that all considerations concerning threshold doses must be made in relation to the *total* dose of exposure, and this furthermore not only to one carcinogen but *to the sum of all carcinogens* which may be present in the human environment.

From the experiments with limited exposure to 4 DAB reported here another conclusion follows, namely that the induction of cancer includes at least 2 processes. The one is the carcinogenic action proper this means the effects of the causative agent, converting normal cells step-by-step into cancer cells, and therefore happening on the cell level. The other is the multiplication of the previously produced cancer cells which, according to the total dose administered, progresses continuously as an autonomous growth, even when the exposure is discontinued and the causative agent is not present any more. Therefore, since two progressive events are apparently involved, the carcinogenesis as a whole is regarded as an accelerated process, which rises to the square or even higher power of the time, as already suggested by experimental observations (6) (7)

These are some aspects and experimental results that I wanted to mention for a better understanding of the problems under discussion before I come now to our experiments with tobacco and tobacco smoke condensates.

The main problems are these of course I tobacco tar or smoke condensate really a carcinogen? And if so what type of carcinogenic substance is contained in it? Does it originate from the pyrolysis? Is it related to higher aromatic hydrocarbons? Or on the other hand, is tobacco smoking only related to lung cancer in an unspecific way being perhaps a mere co-carcinogenic factor or a complete unspecific irritant?

In the discussions of these problems there are so many discrepancies and inconsistencies that it seems highly advisable for me to keep to facts and experimental results and to avoid going any further I

Prof Klein Perhaps you would like t comment on this, Dr Wynder?

D Wynder Actually all I ha e to say I had planned to say tomorrow because all th points which Prof. Druckrey covered we planned to cover in our presentation tomorrow I am delighted to see that the same type of program that we are carrying on in the United States is being carried on by Dr Druckrey in Germany on a different animal system, and I believe that these studies are important enough that different investigators throughout the world not only duplicate these studies but work on different animal systems. Certainly these studies show that tobacco smoke is carcinogenic not only to mice but also to rats. We will discuss tomorrow how we think the carcinogenic effect can be explained on a combination of initiating carcinogens and promoting substances. One of the things we do know of course, is that initiat ing substances in very minute concentrations, i.e. *one microgram, can produce cancer when* followed p by promoting substances. For ex ample it has recently been shown that as little as one microgram of DMBA acted as an initiating carcinogen. And ou current belief is that this is how the polycycli hy drocarbons in tobacco smoke act, because we have shown that if we can remove the hydrocarbon fraction from tobacco smok condensate it loses more than 90 per cent of its carcinogenic activity Let me stress that we believe that it is only acting as an initiating car cinogen. In a recent study that Dr Hoffmann and I published we pointed out that, *by itself* this fraction could account for not more than 3 per cent of the total activity which agrees perfectly with Dr Druckrey's finding — I hav *one question. In our experiment on tobacco ex*tract which was published in 1957 I belie\ we extracted the tobacco with hexane and, ac tually the amount of tobacco extract we obtained was about 3 per cent. At that time we found number of polycyclic hydrocarbons in this tobacco extract. The question I would like to ask you D Druckrey is In you 70 per cent alcohol extraction, how much did you extract there How much tobacco did you obtain on gram basis It is, *of course* quite conceivable that your extract is different from ours. Certainly on the results based pon human studies show ng that tobacco chewers have an increased risk of mouth cancer we would predict tha there must be some carcinogenic effect also in tobacc extract I fact, *even in our experiment we got few tumours* occuring very late And, *of course* I am interested in finding out in what way your extract may have differed from ours.

Prof Dru k ey To answer Dr Wynder's questions, I *should like to say that considering* the problem of initiating and promoting actions we worked purposely with rats. As you certain ly know until now this problem has been shown conclusively to exist only in mice skin, but we have no indication that the same thing happens in the subcutaneous tissue of rats. My personal opinion is, therefore that it would be worthwhile to look for real carcinogen and only after having found this should one search for concomitant factors, cocarcinogens and so on. But everybody has his own way and it is absolutely necessary that everybody follows his own way very strictly W should not forget, however that the cocarcinogenic effect can be shown only on the skin of mice and that there is no such thing in the subcutaneous tissue of rats. — *The second point. Of course, the ex*tractions with hexane and alcohol respectively are not comparable The amount of extracted material was about the same as th amount of *smoke condensate which comes from a cigarette* i.e. in the *order of 20* milligrams per cigarette. We are trying of course to investigate other extracts, too, with other concentrations of alcohol and other solvents in the hope that perhaps it will become possible to extract some danger ous material.

Dr Wynder W studied the same tars as you *have studied, tars A and B and we found* slightly less activity of those two tars than for the American cigarettes. W thought, perhaps, one reason might be that these tars had been denicotinized. I wonder whether it would be possible for your rats to take the total tar including the nicotine or would this be too toxic?

Prof Druck ey No, it is possible And we will do it.

D Carruther I would like to ask Prof Druck rey about his tobacco extracts. Was it extracts of green tobacco leaf or cured leaf? What *is the difference between your condensates A and* B

Prof Dru krey It was leaves as used for cigarette manufacture i.e cured leaf. — Whereas condensate A comes from normal cigarettes, in condensat B it was tried to mak the cigarettes burn more completely the tobacco leaves were cut more fin ly the porosity of the paper was *increased and so on.*

complete as possible, since many experiments suggest that incomplete combustion may be an important factor for the carcinogenicity of smoke condensates. In both groups malignant tumours developed mostly sarcomas at the site of injection (Figure 6) and this occurred in all strains of rats in the same way. In most cases the tumours contained residues of the injected condensate. A transplantation experiment was succesful. One tumour line has been transplanted now in more than 100 generations.

A survey of the results obtained with condensate A is given in Figure 7. The percentage of the surviving rats is plotted on the ordinate and on the abscissa the lifetime in number of days. Each circular dot corresponds to a rat with a malignant tumour in the experimental group the triangular dot in the control group. It is outstanding that in the experimental group, treated with smoke condensate one tumour comes after the other especially in the end of the experiment. As a whole 15 out of the 75 rats developed malignant tumours, corresponding to 20 per cent. Calculated against the 68 rats surviving at the appearance of the first tumour the yield of malignant tumours is 22 per cent

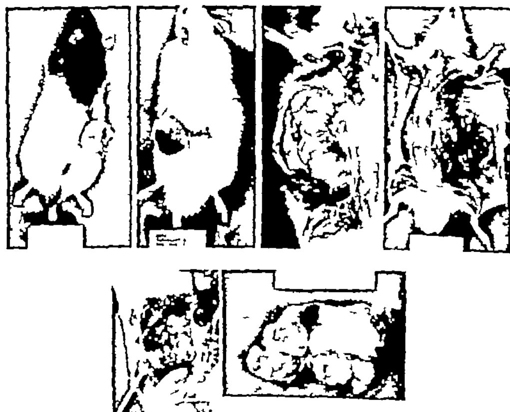


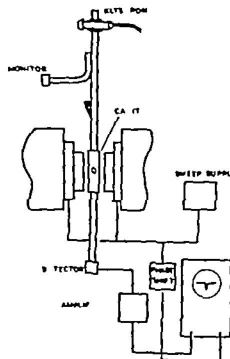
Figure 6. Local sarcomas in rats of different BD-strains produced with cigarette smoke condensate at the site of injection.

stituted into this equation the expression $\nu = 2.8 \times 10^{6}$ H is obtained and hence with the kind of magnetic fields available in the laboratory a frequency of about 10,000 Mc/s is required to detect these free radicals, and this corresponds to a frequency in the radar or microwave range and so radar techniques are employed in this kind of work.

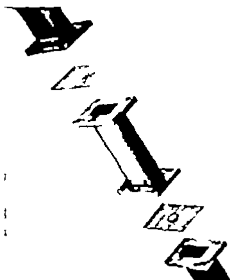
Figure 3 shows the essential features of the equipment. A radar valve called a klystron, is used to produce the high frequency which is fed down the waveguide to a cavity which serves to concentrate the high frequency radiation at this point. The specimen is inserted through the hole, in the middle of this metal cavity The specimen holder is normally in the form of a glass or quartz tube which would contain the condensed smoke of the cigarettes or other free radical material. When it is in position it is bathed in the high frequency radiation and is also held in the strong magnetic field. The resonance conditions are thus fulfilled and by applying a small modulation on the magnetic field the absorption can be traced out on an oscilloscope In this way by simply placing the specimen in the cavity and observing the oscilloscope screen, it is possible to actually see and measure how many of these active radicals are present in the specimen.

So that the details and the possible limitations of this technique can be appreciated Figure 4 shows a cutaway picture of a cavity of very simple form. This is made of a piece of rectangular waveguide with a hole into which the specimen is inserted. An input and an output waveguide feed the cavity and two coupling-holes are formed in thin metal sheets.

For various reasons it is sometimes advantageous to work at low temperatures. Thus if really active radicals are present



F gu e 3 Block diagr m f room temperat electron ... f ... trometer


F gu 4 Phot gr ph f ... ded cavity showing coupling holes and wave guide fe d

treatment	rats number	exposure time days	total dose injected benzpyrene micro g	solvent ml	malignant tumours
benzpyrene	47	800	106	5.5	2 (4 %)
benzpyrene anthracene pyrene	46	900	116	6	4 (9 %)
solvent control	30	800	0	5.5	2 (6 %)

***Table 3** Benzpyrene and mixture of higher aromatic hydrocarbons tested for carcinogenic activity in small dosage by continuous subcutaneous injections in rats.*

sarcoma developed at the site of the injection and one rat died with lymphatic leukemia indicating a certain carcinogenic effect. Therefore, under the conditions of our experiment, a total dose of 116 micrograms of benzpyrene must be considered as on the borderline of the threshold dose. Additional experiments to investigate the dose response relationship of benzpyrene in our rats are under way

The results with pure benzpyrene solutions have to be compared with those obtained with tobacco tar The concentration of benzpyrene in tobacco smoke condensate has usually been found to be of the order of 1 mg per kg With the condensates used in our experiments a lower content was found of about 800 micrograms per kg, too low for an accurate estimation. Recently P P Dikun (10) in Leningrad recommended that one should make use of the fact, that by investigation of solutions in the frozen state at the temperature of liquid nitrogen (−195) the fine structure of fluorescence spectra is obtained. This method he found highly sensitive for the detection and estimation of even small traces of higher aromatic hydrocarbons. Doctor Dikun kindly offered to make a quantitative determination of the benzpyrene content of our smoke condensates, but the results are not yet at hand.

The total dose of condensed tobacco smoke administered per rat in our experiments was 3.2 g Supposing a benzpyrene content of 800 micrograms per kg this corresponds to a total dose of 2.6 μg per rat. Since, with the pure hydrocarbon at a total dose of 106 μg, practically no malignant tumours were produced in contrast to 20 per cent with the smoke condensate under the same conditions, it must be concluded, that the benzpyrene content can explain only about 1 to 2 per cent of the actual carcinogenicity of the smoke condensate. Similarly E. Wynder and G Wright (11) have already stated that the benzpyrene concentration is far too low to account for the carcinogenicity of condensed tobacco smoke.

One may assume that perhaps cocarcinogenic factors are contained in smoke condensate, which promote the carcinogenic action initiated by e.g benzpyrene. However although such cocarcinogenic effects apparently play an important role in the carcinogenesis on the skin of mice, as with tobacco tar (12) there is according to our present knowledge no indica

III INTERPRETATION OF THE SPECTRUM

The information that can be obtained is now summarised, first in general terms and then in relation to the question of the smoke condensate and tars from tobacco

There are two types of information that can be obtained from a simple absorption line. First, as already explained, the area under the line can be integrated and this will give the number of free radicals in the specimen. Information can also be obtained from the width of the line this is somewhat more complicated theoretically and will not be discussed in detail in this paper

In certain cases, however the spectrum is composed of more than a single line and structure is obtained which can be extremely helpful, because it can be used as a method of identification. Figure 8 shows how this originates with one proton. If the electron of the free radical is moving in an orbit which is closely coupled to one proton, then it will not just be affected by the external magnetic field but it will also be affected by an additional component due to the magnetic moment of the proton, according as to whether the particular proton has its spin pointed parallel or antiparallel to the applied field. Hence it is possible to detect the fact that the electron is moving round one proton by the fact that the proton perturbs the energy levels splits them into two and in the same way the actual absorption line observed is split into two instead of being a singlet. Hence an electron interacting with one hydrogen gives a spectrum of two lines.

This reasoning can be followed through Figure 9 shows what happens when the electron interacts with two protons. This will occur if CH$_2$ group is the act

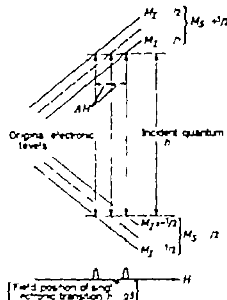


Figure 8 Energy level splitting and resultant hyperfine pattern due to interaction with one proton

group in the radical. There will then be a further interaction with another proton and so each of the original doublets is further split. Thus *four* levels are produced, with the central two overlapping Thus, so far as the transitions are concerned, there are now *three* lines with the central line twice as intense as the outside ones because the two centre levels overlap So in other words if the active radical is a CH$_2$ group a structure of three hyperfine lines will be obtained whereas, if it had just been a CH group only two lines would be observed

Figure 10 extends the reasoning to the case of three protons It will be evident how the spectrum is formed, and in this case *four* hyperfine lines are produced with an intensity ratio of 1.3.3 1



Figure 9 Local sarcomas in rats produced at the site of injections with 70 per cent alcoholic extract of unsmoked tobacco

comas at the site of the injections (Figure 9) The experiment is not yet finished. Up to the present moment 18 rats have showed malignant tumours, 49 died without tumour and 18 rats are still living, some of them with developing tumours (Figure 10) Therefore the tumour yield is in the order of 22 per cent against 20 per cent in the experiments with smoke condensates. This striking carcinogenic effect of tobacco extract is more surprising since the total dose administered 3.2 g

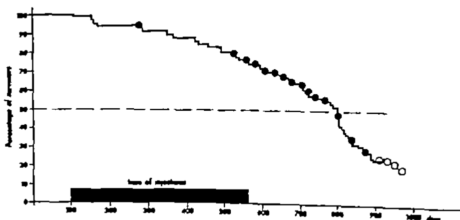


Figure 10 Appearance of malignant tumours and death rate of 75 rats injected with 70 per cent alcoholic extract of unsmoked cigarette tobacco (not yet finished) Black dot malignant tumours Open circles growing tumours.



Fig 12 Electron res nance sp ctrum of d me sityl methyl d cal (Derivative t cing)

two groups shows that the electron is spending most of its time round the central carbon atom interacting with its single attached proton An analysis of each of the two groups of lines shows that they consist of seven groups of five lines. The splitting into five is produced by the four protons attached directly to the rings and the further splitting into seven is produced by the two extreme CH_3 groups which interact much more strongly than the others if the molecule is planar The detailed pattern of activity around the molecule can therefore be deduced in this way

This brief summary of the principles and application of electron resonance has shown I hope, that it is possible first to detect the presence of these active electrons in a compound, and then, in some cases, to deduce where they are located, what the active part of the radical is. The detailed application of this technique to the problems associated with tobacco smok condensate will now be considered.

IV MEASUREMENTS ON TOBACCO SMOKE CONDENSATE

Figure 13 shows the actual apparatus employed to investig te th possibil ty of free radicals being trapped in tobacco smoke. We call this a smoking machine (4) It has four outlets in the form of vertical tubes which are of a size to take a cigarette as an easy push fit The suction pipe at the side goes to a filter pump which is actually turned on and off automatically at an intermittent rate and this is designed to suck at the same kind of rate as a normal human being and with the some kind of force In other words we try and adjust this so that the cigarette ends glow at about the same temperature as in normal cigarette smoking There are now two important parts to this experiment. The first is to deter

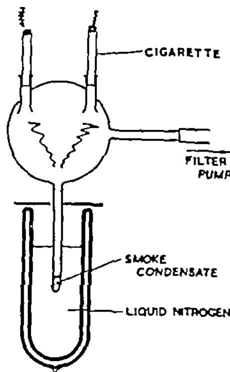


Fig 13 Smoking machine employed to d p f smok cond at f section t t sp from t

sity of the smoke solution was measured quantitatively. Figure 11 shows 3 cuvettes



Figure 11 Fluorescence intensity of benzene solutions containing one puff of cigarette smoke taken by mouth-smoking (left cuvette) and after deep inhaling (right one). The cuvette in the middle contains pure benzene

the middle one contains the pure benzene, the one at the left the solution of smoke after one puff taken by mouth and the one at the right after deep inhaling. The difference is so striking that this simple experiment is very convincing. The quantitative estimation of the fluorescence showed that 85 to 95 per cent of the smoke is retained in the organism after deep inhaling compared to about 15 to 20 per cent by smoking without inhaling. The same results were obtained by E. L. Wynder as reported in his lecture.

Since tobacco smoke is certainly only a week carcinogen, every reduction of exposure should reduce the risk considerably. The differences of the absorbed amounts of smoke, observed with and without inhaling are so striking that I don't hesitate to say that *the risk of lung cancer is not so much a problem of smoking but in the first place a problem of inhaling the smoke*. This explains in the same way the apparent statistical differences in the frequency of lung cancer between cigarette smokers on the one hand and pipe and cigar smokers on the other since the carcinogenicity of the smoke condensates has been found to be practically the same for all of these products (18) whereas the habit of inhaling is related mainly to cigarette smokers.

Nearly all investigations of the tobacco problem have been started with the assumptions 1) that the carcinogenic agents are produced only in the process of smoking and 2) that higher aromatic hydrocarbons, especially benzpyrene compounds, are the main causative substances. This, however, seems to be a prejudice. The results of our experiments confirming the carcinogenicity of smoke condensates also in the species of rats lead to the conclusion, that only about 1 per cent of the effect, or even less, can be explained by its benzpyrene content. Furthermore the comparatively high carcinogenic activity observed with an extract of nonsmoked tobacco suggests that one should look for other carcinogenic substances in the tobacco itself and consider the smoking process not only as a toxicating but rather also as a detoxification process.

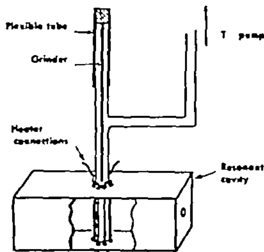
Although these experiments must be duplicated, to test the reproducibility in other species too, the results should stimulate further investigation and open new possibilities of reducing the carcinogenic risk of tobacco products, especially cigarettes.

It is my optimistic feeling that technical problems can in principle be solved. I am convinced that it will become an interesting and stimulating field for the chemists and technologists of the tobacco industries to try every method of reducing the cancer risk of cigarettes as far as feasible. Filters can certainly not be considered as the solution to the problem. Cigarette smoking is a habit and it seems unrealistic to change such habits of man. But young people should be warned against an early start of cigarette smoking since the high impor-

pect to have a variety of different types of free radicals present. The fact that there is no specific elimination by one particular form of treatment confirms this.

The more stable radicals, which exist after warming and standing at room temperature can be studied in detail from several points of view One can show that by pyrolyzing all types of organic matter quite high concentrations of these stabilized radicals can be obtained (5) It is envisaged that these radicals have the form indicated in figure 1 (c) Thus they consist of condensed carbon rings and because these are condensed conjugated ring systems, it is easy for the unpaired electron to move in a delocalised orbital which is the condition one wants for stabilizing the electron.

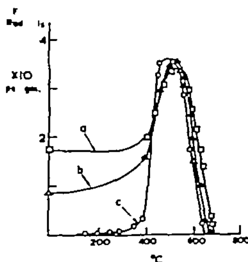
Figure 14 shows an apparatus that has been used for extending this investigation in a general way (5) This apparatus was designed for pyrolyzing all types of material, and consists of a heating element around a quartz tube within a cavity This is filled with different types of organic material, such as sugars and the like, and this would then be heated to known temperatures and the production of free radicals during the heating process would be studied.



F'gu 14 App us for heati g pecimen in situ i th sonan avity

Figure 15 summarises the results obtained.

It is evident that in all these cases an apparent maximum is obtained in the free



F'gu 15 F ee adical concent ation prod d on pyrolysis of ganic matter

radical concentration at about 600°C. It is of course in about this temperature region that cigarette smoke is produced The production of free radicals is therefore not a specific action, they are not produced by the pyrolysis of one particular material, but their formation is a general property of organic material condensed rings being formed which tend to stabilise the unpaired electrons.

References

1 Druckrey H Klin. Wochenschr *22* 532, (1943)

2 Druckrey H K. Küpfmüller Z. Naturforschg *3b* 54 (1948)
Druckrey H u. K Küpfmüller Dosis und Wi kung, Editio Cantor A lendorf Wrtbg 1949
Druckrey H. u. D. Schmähl, Mediz Klinik *55* 648 (1960)

3 Druckrey H. Arzneimittelforschg *7* 449 (1957)

4 Haddow A R. J C. Harris, G A R. Kon and E. M Roe, Philos. Transact. Royal Soc *241* 147 (1948)

5 Schmähl, D R. Mecke J Z. f Krebsforschg *61* 230 (1956)
Druckrey H. Arch. exp. Path. u. Pharmakol. *238* 67 (1960)

6 Blum, H F Carcinogenesis by ultraviolet light, Princeton University Press 1959

7 Druckrey H Arzneimittelforschg. *1* 383 (1951)

8 Wynder E. L., E. A. Graham and A. B. Croninger Cancer Res. *13* 855 (1953)
Wynder E. L. and D Hoffmann, Cancer *12* 1079 (1959)

9 Druckrey H., Strahlentherapie *93* 165 (1954)
Oncologij 7 155 (1954)
Acta Unio I tern. Canc *10* 29 (1954)

10 Dikun, P P Oncologij (U.S.S.R.) 5 672, (1959)

11 Wynder E. L. and G Wright, Cancer *10* 255 (1957)

12 Gellhorn, A. Cancer Res. *18* 510 (1958)
Roe F J C., M. H. Salaman and J Cohen, Brit. J Cancer *13* 623 (1959)

13 Sanghvi, L. D K. C. M. Rao and V R. Khanolkar Brit. Med. J *4922* 1111 (*1955*)

14 Cooper R. L. and J M Campbell, Brit. J Cancer *9* 528, (1955)

15 Kennaway E. L. and A. J Lindsey Brit. Med. Bull. *14* 124 (1958)

16 Lyons, M. J J F Gibson and D J E. Ingram, Nature *181* 1003 (1958)

17 Schmähl, D U Consbruch u. H. Druckrey Arzneimittelforschg. *4* 71 (1954)

18 Croninger A., E. A. Graham and E. L. Wynder Proc. Amer Ass. Canc. Res. *2* 289 (1958)

DISCUSSION

Prof Klein Prof. Druckrey when you are dealing with rats how do you manage to localize the site of injection? I think this must be problem.

Prof Dru k ey Of course, it is problem, and we have the same type of problem in, for instance the skin painting technique but with little experience it can be done properly

Prof Klein You don t think that there is difference in this respect between pure carcinogens and tobacco smoke condensate I mean the volumes injected and so on.

Prof Dru krey The olumes are always the same. W hav taken as principle only to hav one variable factor in our experiments.

Prof Klein Provided there are promoting substances present in the smoke condensate, do you think that they would be distributed over larger area

Prof Druckrey This may be so, but on the other hand the positive outcome of our experiments with extracts of unsmoked tobacco shows that either must this cocarcinogen be present already in the extract or w have to deal mainly with pure carcinogenic action and the cocar cinogen is only increasing the effect.

Prof Klein Are the types of tumours obtained exactly the same with tobacco extract and with smoke condensate?

Prof Druckrey Exactly the same. The tumour yield was greater with tobacco extract than with smoke condensate and I think it is ery plausible to chemist that combustion process must be considered not only as toxication process but also as detoxication process since we know that many substances are destroyed in the combustion and the more so th more complete the combustion is. I think Dr Wynder will agree with me that it is advisable to render the combustion in tobacco smoking as complete as possible.

The actual role of the free-radicals in initiating carcinogenesis is not too clear. There is experimental evidence from some of the plastic work of Oppenheimer (7) that more tumours are produced if irradiated plastics containing free radicals are implanted into mice than if unirradiated material is used. So that there is *some* evidence, relatively direct evidence, that free radical containing material has a direct link with carcinogenesis, but as far as our own measurements are concerned, all we can claim to have shown in this work is that there are both active and stable free radicals present in cigarette smoke condensate.

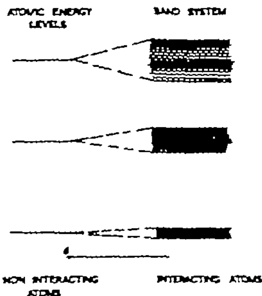


Figure 19. Formation of energy band system in the solid state

V POSSIBLE ROLE OF A SEMICONDUCTOR MECHANISM

Another theory is being put forward *quite* extensively at the moment on the role of electrons in carcinogenesis (8) (9). This suggests that no actual free radical need be present, but what must be present is a *mobile* electron. It does not matter if it is actually unpaired as far as the whole of the compound is concerned, but it must be mobile and able to move about over the whole molecule. It is, in fact, a "semiconductor" theory applied to protein molecules and the basis of this theory will be first outlined, and then experimental evidence which does appear to support this theory will be summarised.

Figure 19 shows how a band system is formed in the solid state.

The actual energy levels of the individual atoms are shown as distinct discrete levels on the left-hand side. Then as the atoms come together in a solid—such as the simple case of a metal—their individual energy levels are perturbed into a band system as shown on the right, so that they are smeared out and not just individual levels. The point of the present theory is the postulate that the same kind of thing can happen in a protein, that the interaction between the individual atoms of the protein will produce a band system over the molecule and not just discrete energy levels attached to individual atoms.

Figure 20 summarises the different kinds of end effect that such interactions can produce. If the bands are well separated as on the left, and the bottom band is filled with electrons, as it would be for a saturated compound, then the electrons cannot move, the only way they could move would be to jump from the bottom to the top band system. They have not sufficient energy to do this, and hence the material is an insulator. The other extreme to this is a metal where the two band systems overlap as shown on the extreme right of the figure. The interesting case however is a semiconductor where the energy gap is relatively small and it is possible to excite an electron

Electron Resonance Studies of the Free Radicals Produced in Tobacco Pyrolysis and in other Related Compounds

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I INTRODUCTION

I think I should explain that this lecture will be rather different from the previous two since it deals with some of the possible mechanisms of carcinogenesis rather than what I would call the "purely experimental proof of correlation" we have had this morning. In this connection it should be stated at the outset that what I am going to say and the results I am going to discuss, as they apply to tobacco smoke and carcinogenesis, are considerably more speculative than the experimental results that have been previously reported. This must be so because one is trying to test out different ideas and different theories, and they may or may not be right we are not in a position to dogmatise yet. In particular the paper considers two theories of electron interaction. One is that free radicals may have some part in the mechanism of carcinogenesis. The other is that free radicals themselves may not be necessary but that a high mobility of electrons in carcinogenic compounds is an essential requirement. I want to try and discuss both of these points of view and review the experimental evidence in support of them. I also hope to discuss how this concept might explain theoretically what the actual mechanism of carcinogenesis involves.

Being a physicist I probably tend to approach this from the physicist's angle, and the contribution we have made is to apply a new *technique* to this study a technique which can be used to study free radicals and which can also be used to give information on mobility of electrons in these highly conjugated systems.

Now I will start by discussing first the nature of free radicals, and the effect that they may have on the carcinogenic activity I am not quite sure how familiar all of you are here with the idea of a free radical and if those of you who are well acquainted with the subject will excuse me for a few minutes, I will go over the general concept of free radicals, what they are, what they can do and how one can detect them and then go on and consider the actual application to the tobacco smoking problem.

The first figure shows three examples of different free radicals. Figure 1(a) is one of the simplest types of stable or semi-stable free radical. It has a benzene ring with four hydrogens round it and an oxygen atom at each extremity It is, in fact,

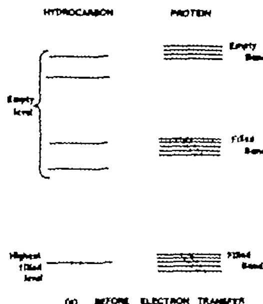
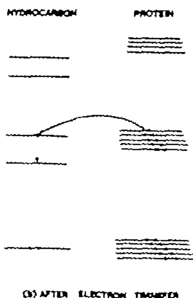


Figure 21 Mechanism of carcinogenesis by electron transfer between protein band system and active hydrocarbons. (a) Before complex is formed (b) After complex is formed



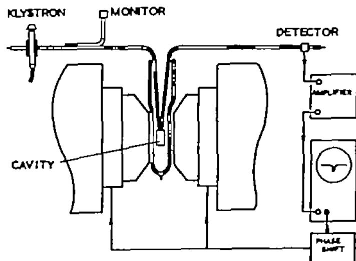
As a result of this complex formation a free electron has been left in the protein which can wander about through the π-band system over the whole of the molecule.

VI EXPERIMENTAL EVIDENCE FOR "SEMICONDUCTOR THEORY"

The actual conditions for the interaction outlined above to occur are relatively crucial. The energy levels of the hydrocarbon must fall in the correct range as determined by the protein band structure.

Table I is reproduced from a paper by Mason (9) where he does actually make the comparison between the calculated energy gaps and the observed carcinogenicity of various hydrocarbons. If these columns are studied in detail, it will be found that the compounds which are active, as indicated by the positive marks in the last column all have an energy gap with a value of between 1.11 and 1.18. The units employed here are the units of exchange integral which have a value of 2.8 eV. So if one puts these units in, it is just the hydrocarbons which have an energy gap of about 3 eV which are the active ones. This evidence is strong support for the semiconductor theory, i.e. that the hydrocarbons which can provide *an energy level to disassociate the electron* from the protein, and hence leave a mobile electron on the protein, are just the ones which are carcinogenically active.

It will now be shown how the electron resonance measurements also seem to confirm this. There is another way one could detect such a forbidden gap, and this is to try and measure the energy gap in the proteins themselves. If we can show that this is also about 3 eV this is further confirmation of the general theory



F gu 5 Block diagram of low temperatur le tron sonanc pectrometer

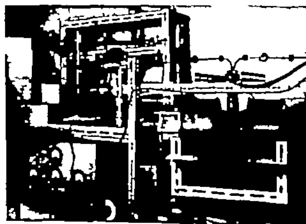
and they are to be studied before they react with one another a possible technique is to freeze them to very low temperatures as quickly as possible Figure 5 is a block diagram of the kind of low temperature apparatus that can be used for this purpose This is basically the same as the first spectrometer except that a Dewar containing liquid nitrogen surrounds the specimen, but the radiation is fed in and out as before, and the absorption is finally displayed on the oscilloscope

Figure 6 shows a photograph of one of these low temperature resonators and the specimen is placed centrally on the bottom plunger which is then screwed up into position.

A photograph of the complete equipment is shown in figure 7 as typical of such an electron resonance spectrometer



Figure 6 Photogr ph of Q-band cavity sonator befor inserting sample holder



F gure 7 Photograph of complet pectrometer run

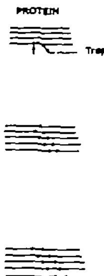


Figure 22 Electron excitation in protein by U V irradiation.

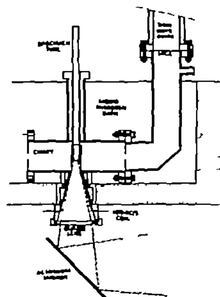


Figure 23 Apparatus used for U V irradiation "in situ" in the spectrometer

this energy gap is the same as that between the bottom bands, and if it can be shown that in fact 3 eV energy are required to excite the electron in this case further confirmation of the theory will be obtained. This can be done by irradiating the protein in the electron resonance spectrometer and determining what wavelength is required to produce an extra number of electrons in the upper band system.

Figure 23 shows the kind of equipment that is used for such irradiation "in situ" U V radiation can be focussed on to the specimen in the cavity and the occurrence of extra unpaired mobile electrons can be studied as they are formed.

If such irradiation is carried out at low temperatures it is possible that a number of electrons, which have been excited into the higher level, will fall into a "trap produced by an additional proton attached to the main polypeptide chain (11) In this case electrons resonance signals will be obtained when such samples are studied after irradiation at the low temperature, but on warming the electrons in the traps will be reexcited to the upper level and then decay to the ground state. These features are illustrated in the preliminary results we have obtained by irradiation of various proteins (12)

Figure 24 shows spectra that have been obtained after irradiation of tyrosine, leucine, and egg albumin It is evident that no definite signal is observed when the simple amino acids are irradiated with a wavelength of 3650 Å but the egg albumin shows quite a large resonance absorption. This absorption is found to disappear completely on warming the sample to room temperature as can be seen in Figure

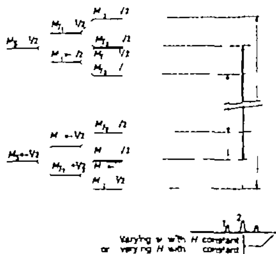
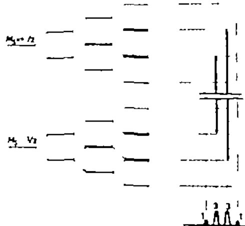


Fig 9 Energy level splitting and resultant hyperfine pattern due to interaction with two protons.



Figur 10 Energy levels and resulting pattern for interaction with three protons.

This characteristic hyperfine structure acts as a finger-printing process. Hence it is possible to deduce not only how many radicals are present in the substance, but, under suitable conditions, it is also possible to determine what they are, i.e. what are the actual active groups in the compound.

As an illustration of this, the case of the p-benzosemiquinone radical may be taken. The formula for this is shown in figure 1( ) and since t has *fou* protons round the benzene ring it follows that *five* hyperfine lines are expected, with an intensity ratio of 1-4-6-4-1

Figure 11 is the electron resonance spectrum of this radical (2) and the five lines can be clearly seen with their intensity ratio as predicted.

This method of analysis can not only be applied to simple radicals but also to the more complicated radicals such as the di-mesityl methyl radical of figure 1(b) Figure 12 is a derivative tracing of the spectrum obtained from this radical (3) An analysis of this shows where the unpaired electron is moving and enables the detailed molecular orbital to be evaluated.

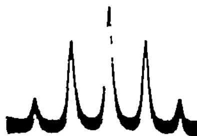


Figure 11 Observed hyperfine pattern of th benzosemiquinone adical.

The main features of the spectrum can be readily interpreted even if the details are ignored. The marked splitting into

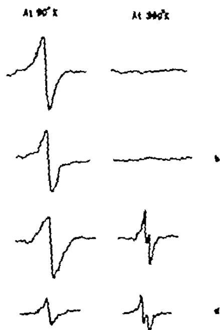


Figure 26 Effect of warming irradiated egg albumen samples prepared in different forms (a) The protein in aqueous solution (b) [illegible] dried polycrystalline form. (c) Evacuated polycrystalline form. (d) Polycrystalline sample suspended in alcohol.

26(c) Exactly the same result is obtained if a suspension of crystals in alcohol is used instead of the normal solution in water as shown in Figure 26 (d) The conclusion drawn from this measurement is that interference with the loosely bound water molecules, attached to the protein, radically alters the semi-conductor band system and, on warming the electrons leave their initial traps and become permanently locked in some form of crystal defect. This conclusion seems to confirm the recent ideas on the importance of "ordered" structure in the water molecules associated with bio-chemical systems

VII SUMMARY

It will be seen that the later work reported here is only of a tentative nature at the moment and a systematic series of experiments are being undertaken to try and confirm the various suggestions or hypothesis that have been made. On the other hand there does appear to be quite definite evidence for the excitation of electrons in some protein molecules to an excited band system, and if this is taking place then electron mobility is readily available in such compounds. The striking feature of these results in our present context, is that the apparent energy gap in such proteins is about 3.2 eV and this is just the amount measured for the carcinogenically active hydrocarbons.

It would, therefore, appear from the electron resonance studies that carcinogenically active molecules such as those found in tobacco smoke condensate, contain both active and stabilised free radicals and also hydrocarbons which may form complexes with protein molecules and, in the process, produce highly mobile electrons. There is still insufficient evidence to state categorically that either of these mechanisms is, in fact, the one mainly responsible for carcinogenesis, but it seems highly probable that either or both, may be playing a very active part in the process.

mine if ctive unstable radicals have been formed in the smoke If only stable radicals are present, all that is necessary is to collect the smoke and when sufficient is obtained put it in the spectrometer and see if a signal is observed from the stable radicals. Some of these radicals may be very unstable however and they will therefore only exist for a few seconds, or less than this. Therefore the experiment was designed to see if we could detect both of these kinds of radicals. The idea is that the bottom finger dips down into liquid nitrogen, so that all of it is kept extremely cold It appeared that as far as could be told from the rough measurements, it took about two seconds for the smoke coming from the cigarette end to arrive in the bottom finger and be deep-frozen. Once the radicals have been cooled down to the liquid nitrogen temperature they are ery unlikely to react, however active they normally are. Thus, by employing this technique all the radicals which have longer than, say two seconds lifetime are being trapped in the cold finger After collecting about one gram quantity of material, most of which will in fact be just ice frozen carbon dioxide, which are the main products of our combustion, this is then transferred, being kept at liquid nitrogen temperature all the time, into the electron resonance spectrometer where the measurements are also carried out at liquid nitrogen temperatures. When this was done t was discovered that this condensate contains a relatively large quantity of free radicals, of the order of 6×10^{16} per gramme. Of course, in molar concentration this is not very much, but in comparison with other naturally occurring quantities t is relatively high concentration. It is considerably higher than would be obtained in any barley lea es, or in normal metabolic tissue.

Having measured the concentration in the actual condensate at liquid nitrogen temperature the specimen is then warmed up to room temperature and left at room temperature for ten or fifteen minutes, so that any active short-lived radicals can react together and disappear It is then cooled down again, refrozen and the concentration remeasured at liquid nitrogen temperatures. The results of this indicate that in fact fairly high proportion of the free radicals are lost when the specimen is warmed. It is rather hard to obtain reproducible results because of the varying amounts of carbon dioxide and water but it would appear that in fact the signal goes down to about a third of its alue for the whole of the frozen condensate. The conclusion from this experiment is that there are quite an appreciable number of radicals present in the smoke condensate and over half of these, at any rate, are of the active or short-lived type.

The next step was to separate out the water etc. and take the actual tar fractions and treat these in different ways and see if there was any indication that the radicals went with one kind of tar rather than in another These experiments showed that just washing with water reduced the concentration by about 10 per cent, washing with alkali reduced the concentration by 50 per cent, and washing with alkali and then acid reduced the concentration by 72 per cent. The conclusion one draws from this is that there must be several different types of radical present. In other words, it is not just *one* kind of free radical that is present in this condensate, but there are a variety I think that one would expect this, i.e. that in the products of pyrolysis different numbers of condensed rings are formed with different chemical groupings round the edges and quite a number of these might easily become free radicals and hence we would ex

Prof. Ingram. Yes, I agree this is one of the points one has to face here. But I think you have got very different order transition probability. In your ordinary transitions you are dealing with molecular vibrations, whereas here one is looking at the interaction across the polypeptide chains, and I think one would expect a much smaller absorption coefficient. Though on the other hand, if this is true it is this one which excites your electron into an unfilled level and not your larger absorbing molecular vibration.

Dr. Lagercrantz. I should like to ask Prof. Ingram a question about your carbon blacks. Do you suppose that they are wholly inert, or can you transfer electrons from this low temperature carbon? Is it possible to use them as an initiator in a polymerization? I remember that you have written in your book about the polymerization of rubber. The theory is not complete or clear and some rubber people maintain that carbon black is added only for its mechanical properties in the polymerisate.

Prof. Ingram. I think the answer there lies in your own words. The theory is not clear. It seems as if they will react say with incoming paramagnetic gases and also transition group complexes so they are not entirely inactive in that way. And this is why I think that, if one relates this back to the question of possibility of carcinogenic activity from the stable radicals, although when they are absorbed in a lung tissue they may not be capable of doing very much active damage I think, under given conditions they may initiate something like polymerization. So I think the answer to your question is that they do react in certain ways, such as initiating polymerization although they are not anything like as active as what one would normally call a free radical in solution.

Dr. Lagercrantz. I had another point of view too. In the presence of carbon blacks in tobacco smoke you would have toxic substances adsorbed on the carbon. Do you think this means a detoxication process?

Prof. Ingram. It may be so that they act indirectly by making it easier for certain other things to be absorbed, because they appear to be linked with the process of absorption. This may be another way by which they could come in, but I do not know of any direct evidence either way. It is only a possibility.

Dr. Lagercrantz. Steiner in Chicago has shown that as long as the carbon blacks were present the carcinogenic substances were inactive.

Prof. Ingram. It might be true that they may act that way. This is an interesting possibility. Free radicals will act as scavengers for each other and they may also act by immobilizing electrons which would otherwise be free. So that it may be that free radicals in cigarette smoke make it less harmful.

Figure 16 shows the free radical concentration plotted against the percentage of carbon in the resulting products. The graph is plotted on a log scale and a very rapid increase in radical concentration is obtained as the percentage carbon increased to 90 per cent. This again suggests that the production of the condensed polycyclic rings is the essential mechanism in the formation of the radicals.

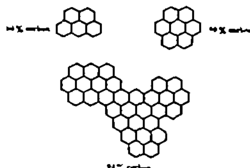


Figure 17. Size of condensed carbon rings as determined by X-ray analysis.

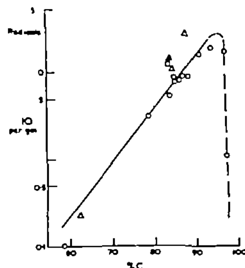


Figure 16. Free radical concentration versus per cent per carbon of pyrolysed specimens.

Figure 17 shows how the size of these condensed ring systems varies with percentage carbon content (6)—which is a summary of X-ray results on these types of pyrolysis products. It is evident that in the region where high radical concentration is observed, large numbers of condensed carbon rings are also obtained. Hence it appears that the stable radicals in the smoke condensate are certainly linked with the large number of condensed rings. The word "stable" should be explained. They are stable compared with the very reactive ones which, say, react and disappear after two seconds. On the other hand these "stable" radicals will react in some kind of way and Figure 18 shows one way in which this occurs.

This figure shows what we call the oxygen effect. The top left-hand signal is as observed under vacuum, and when oxygen is admitted, a decay of the signal is observed. Therefore the electrons in the polycyclic rings must be interacting with the incoming gas.

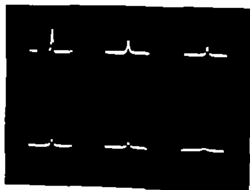


Figure 18. Effect of oxygen on free radical in pyrolysed products.

that the other monkey escaped! In other words, we have often used too few cases or too few experiments. It is quite different in the field of lung cancer I would say that probably there has never been such a massive line of statistical and epidemiological data as in the field of smoking and cancer of the lung

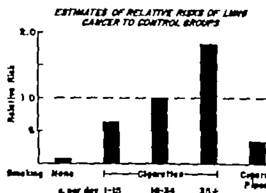


Figure 1

Figure 1 represents a study on relative risk from a retrospective study which shows that the more a person has smoked, the greater is his risk of developing lung cancer The first of these studies Dr Graham and I published in 1950, and since that time more than 25 similar studies have been published in 7 different countries, invol ing more than 6 000 lung cancer patients. Without exception, they have all shown that the more a person has smoked, the greater is his risk of developing cancer of the lung You will note that cigar and pipe smokers run a lesser risk than cigarette smokers, though the risk is greater than for nonsmokers. I believe, in agreement with Dr Druckrey that this is probably due to the fact that cigar and pipe smokers rarely inhale.

In 1954 Drs. Hammond and Horn believed that these retrospective studies, that is to say studies based upon people who already had lung cancer had certain elements of bias and they felt someone should do a prospective study

Data from Hammond and Horn demonstrates the fact that the very heavy smoker has a 60-fold increase in the risk of lung cancer over the nonsmoker (Figure 2) To those of you who are not familiar with the enormity of these statistical differences, let me give you one example We know that single women have a greater risk of developing breast cancer than married women, yet this risk is only 50—75 per cent greater and we all regard this as quite significant. But here you will note that the risk of the smoker who smokes 2 packs of cigarettes or more per day is nearly 7 000 per cent greater than that of the non-smoker a difference that really staggers the imagination! You will also note, and this again is important, that among 32,392 males who did not smoke, the incidence of lung cancer was only 3 4 per 100 000 or so low that if this were the incidence of lung cancer in the general population, we would not sit here today discussing this problem.

Hammond and Horn also showed the risk of lung cancer in urban and rural populations after standardisation for cigarette consumption (Figure 3) Certainly cancer of the lung is more common in urban than in rural areas but as this study shows, part of this difference is due to the fact that the American city population smokes more cigarettes than the rural population A small difference remains—this could be due to air pollution or more likely due to certain occupations such as welders, painters and hot metal workers which are more common in cities than in rural areas.

Figure 4 shows the same results from Doll and Hill, who took British physicians as a study group again a prospective

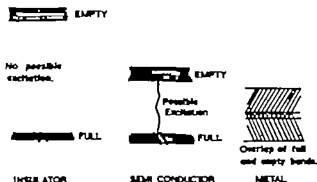
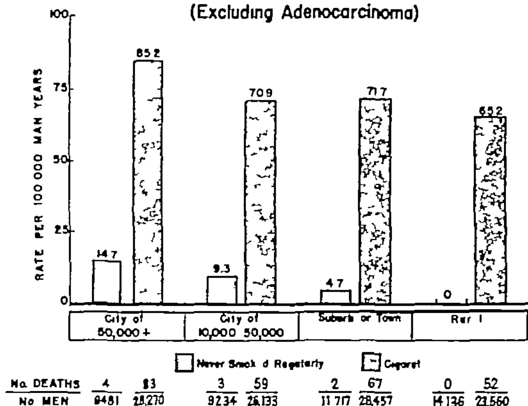


Fig. 20. Different energy band systems for insulators, semiconductors and metals.

from the top level of the bottom band up to the bottom of the top band. If this can be done then the electron can move about freely in this top band. There is also a hole that can move about freely in the bottom band. The important point so far as this is related to the mechanism of carcinogenesis is that if an electron can be excited to the top band, then it can move around the whole molecule in this π-band system, and hence it is available whereever it is required for the particular mechanism that is postulated.

Evans and Gurgley (10) have carried out some detailed calculations on typical proteins and have determined the actual difference in energy between the first three *bands that would be obtained in such a* protein semi-conductor. If the energy at the bottom of the bottom band is taken as zero, then it has a spread of 0.13 eV and there is a jump to the bottom of the next band of about 3 eV; this has a spread of about 0.3 eV and then there is another jump again of just about 3 eV up to the next band. The important point is that it would appear that, in such proteins, semi-conductor band systems exist with about 3 electron volts between each pair.

Figure 21 shows how this can be related to a possible mechanism of carcinogenesis. The band system of energy levels is shown on the right and the levels on the left are those of a hydrocarbon which is carcinogenically active. The change in electron configuration that occurs when these two come together is now envisaged. Before any interaction takes place the protein molecule has two bands filled and is therefore not acting as a conductor at all. The electrons cannot move about over the system and therefore on our postulate they cannot produce carcinogenic activity. If we can dispose of one of these electrons however, then the one left in the half empty level will be free to wander about over the whole of the molecule, and so produce carcinogenic activity. The removal of one electron can be accomplished if the hydrocarbon comes up to form a complex with the protein, and if one of its levels lies within the energy range of the central band system of the protein. There is then a high probability that the electron will jump across from its protein to the hydrocarbon part of the complex, as shown in figure 21(b).



F g 3

cause it must be a genotype that has been changing in recent years it must be a genotype that must cease as one ceases to smoke it must be a genotype that varies from country to country

Figure 5 show you one other thing that this genotype would ha e to do We stu died a religious group in Los Angeles. As you know Los Angeles has a major problem in air pollution The Seventh Day Adventists are a protestant group that was formed in 1863 one of their bylaws prohibits smoking and drinking Dr Frank Lemon and I did a study among the Seventh D y Adventists and indeed found that 99 per cent of Seventh Day Adventists males are no longer smoking once they join the church. Then we studied their rates of cancer and compared them with a control population. You will see that there are only two areas where there is a major difference in expected and observed rates. Cancer of mouth lung, esophagus and larynx and, to a lesser extent, the bladder all of which are considered to be related to smoking In fact, we found only two Seventh Day Adventists with lung cancer and both used to be heavy smokers prior to joining the church The in cidence of cancer of the lung among

TABLE I

Molecule	E	E_2	E_4	E	Activity
Benzene	2.0000	2.0000	3.0000		–
Naphthalene	1.2361	1 6180	1.9208	2.2361	–
Anthracene	0.8284	1 4142	1 4142	1 8284	–
Naphtacene	0.5899	1.07?4	1.2950	1 4885	–
Pentacene	0 4394	0.8377	1.2197	1.2197	–
Phenanthrene	1.2105	1.3743	1 7476	1.9110	–
3 4 Benzophenanthrene	1 135?	1.2297	1.5676	1.6910	
Chrysene	1.0402	1.3124	1.3954	1 7365	–
1.2 Benzanthracene	0.9046	1 1673	1 4523	1 6179	?
Pyrene	0.8901	1.3244	1 4450	1 6920	–
Triphenylene	1.3681	1.5634	1.9696	2.0313	–
Pentaphene	0.8743	0.9580	1 4732	1 4732	–
Picene	1 0038	1 1822	1.3614	1.5019	–
Perylene	0 6946	1.3473	1.3473	1.3473	–
1.2 3 4-Dibenzanthracene	0.9982	1.2131	1.2899	1.5940	–
1.2.5.6-Dibenzanthracene	0.9470	1 1575	1.2601	1.5431	++
1.2 7 8-Dibenzanthracene	0.9834	1 1097	1.365?	1 4917	+
3 4.5 6-Dibenzophenanthrene	1.0709	1 1922	1.3227	1 6027	–
3 4 Benzpyrene	0 7425	1 1730	1.3712	1.3712	++
3 4 8.9-Dibenzopyrene	0 6054	1.0960	1 1314	1.3027	+++
1 12 Benzoperylene	0.8784	1 1235	1 4329	1 4329	?
Coronene	1 0784	1.0784	1.539?	1.539?	–
Anthanthrene	0.5818	1.0409	1 1657	1.3944	–
Diphenyl	1 4092	1 7046	1 7046	2.0221	–
p-Diphenylbenzene	1 1853	1.5926	1.5926	1.5926	–
m-Diphenylbenzene	1.3243	1 4275	1 6622	1 6622	–
o-Diphenylbenzene	1.2206	1 4346	1.6103	1 6103	–
1.3 5-Triphenylbenzene	1.3243	1.5681	1 6622	1 6622	–
Styren	1.3242	1.6622	2.0764	2.7979	–
Stilbene	1.0086	1.5043	1.5043	1 6577	–
Biphenylene	0 8901	1.3244	1 6920	1 7923	?
2.3-6.7 Dibenzofluorene	0.9687	1 0107	1 1518	1 6211	?
3 4.5.6-Dibenzofluorene	0 7466	1.2002	1.2151	1 4433	–
1.2 7.8-Dibenzofluorene	0 8326	1 1848	1.3793	1.5207	+?

This table is taken from the article by R Mason in Natur 181 822 (1958) by kind permisno of the author and publishers.

Figure 22 shows how this may be done by taking a protein and irradiating the sample with ultraviolet light. If the U V quanta have the correct energy the elec tron can be made to jump from the second to the top band.From the calculations (10)

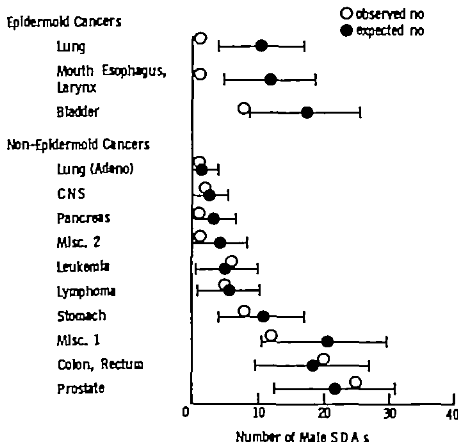


Fig. 5

dustry they would almost make you believe that such condensate doesn't exist. We take the smoke condensate and dissolve it in acetone in a 50 per cent concentration and apply this material to our experimental animals.

Figure 8 shows a mouse with a typical cancer. We have obtained cancers in three different strains of animals. The average mouse gets about 60 mg per application three times a week, amounting to about 10 g of tobacco smoke condensate a year.

Figure 9 shows a summary of our first experiment, that I published together with Drs. Graham and Croninger in 1953. You will note that 59 per cent of the animals developed papillomas and 44 per cent of the animals developed cancer. A few years later Passey in England, stated that he was unable to repeat the experiment. What really happened was that Passey applied too weak a concentration of tobacco smoke condensate to his animals. Of course since tobacco smoke is only a

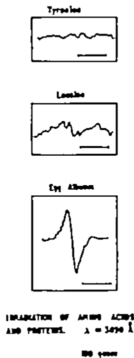


Fig 4 Electron esonan signals obtained after U V irradiation of amino acid and protein sample at low temperatur

tation to a conduction band, followed by electron trapping is taking place in the egg albumin. Further experiments indicate that the presence of loosely bound water molecules form an essential part in this mechanism. This is illustrated by the results shown in Figure 26

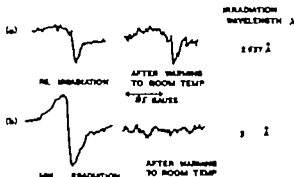


Figure 25 Eff ct f warming periments to room temperatur ( ) Signal due t irradiation da mage emains. (b) Signal due to xcited elec tron decays.

25 The fact that this particular type of signal is not due to irradiation damage of the molecule was demonstrated by irradiating these compounds with the higher energy 2537 Å wavelength. In this case, all the samples show the same kind of signal which remains after warming to room temperature as shown at the top of Figure 25

It is also noticeable that the signal obtained from the irradiation damage is smaller than that produced by the 3650 Å irradiation for the egg albumin. This confirms that the latter is a resonance process.

These results seem to be quite definite evidence that some such process as exci-

This summarises the effect of warming the egg albumin samples irradiated with a wave-length of 3650 Å. The first set of spectra are the same as those shown in Figure 24 and are for the solution of the protein in water The complete disappearance of the resonance signal on warming is clearly seen in this case. Exactly the same results are obtained if a polycrystalline sample is irradiated at liquid nitrogen temperatures and then warmed to room temperature as shown in figure 26(b) If however a polycrystalline sample is evacuated before deep-freezing and irradiation the initial signal is obtained, but on warming a permanent signal remains with a doublet structure as shown in Figure

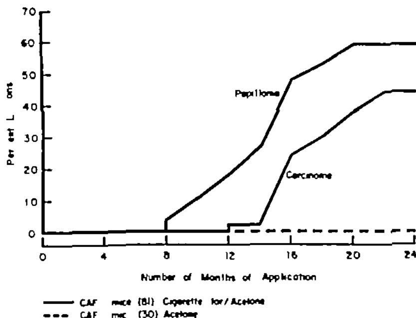


Figure 9

Cancer Rates with Different Tobacco Products – Swiss Mice

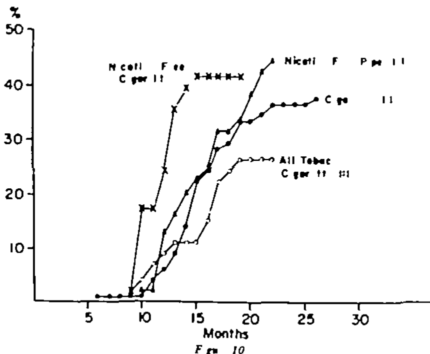


Figure 10

References

1 Ingram, D J E., "Free Radicals as Studied by Electron Spin Resonance Butterworths Ltd London 1959

Venkataraman, B. and Fraenkel, G K., JACS 77 2707 (1955)

3 Jarrett, H. S. and Sloan, G J J Chem. Phys. 22 1783 (1954)

4 Lyons, M. J Gibson, J F and Ingram, D J E Nature 181 1003 (1958)

5 Austen, D E G Ingram, D J E. and Tapley J G Trans. Faraday Soc. 54 400 (1958)

6. Hirsch, P B., Proc. Roy Soc. A. 26 145 (1954)

7 Oppenheimer B. S., Oppenheimer E. T Stout, A. P Danishefsky I and Eirch, F R., Science, 118 783 (1953) and Cancer Research, 15 333 (1955)

8. Szent-Gyorgi A., N ture 148 157 (1941)

9 Mason, R., Nature 181 822 (1958) and Discussions Faraday Soc 27 129 (1959)

10. Gergley J and Evans, M. C., Biochim. et Biophys. Acta. 3 188 (1949)

11 Longuet-Higgins, H. C., Arch. Biochim. Biophys. 86 229 (1960)

12. Allen, B T and Ingram, D J E., Archives des Sciences. Genera. 13 (in press)

DISCUSSION

Prof Dru krey May I ask two questions, Prof Ingram — Are these free radicals formed also in normal metabolic processes? And secondly don t you think it possible that the free radicals may hav the property of being both toxic and detoxicating?

Prof I gram It is certainly ery true that radicals do appear to hav part in all forms of metabolic activity But I think there is one important point here that is, say naturally occurring organism the chemical groups round the particular radical may be such as to insure tha that radical can only combine chemically in certain way whereas if you suddenly inject into system variety of unspecified radicals which may have quite different chemical properties from those which the organism is normally dealing with then these may upset the normal metabolic process. I certainly agree that they may help or they may hinder but if you are injecting into system variety of free radicals which hav no inherent relation before, then I think it is probable that those will tend to damage rather than the reverse.

Prof Theorell May I ask just one technical question As far as I could see indicated on your last slide you had irridiated protein, eggalbumin, at 3650 Å. As far as I can understand, proteins will not be able to absorb energy of this frequency

Prof I gram I fact I agree that the absorption band is ery small there. But I think this possibly underlines the point, because the sensitivity is ery high and one only needs very small absorption to produce this effect. If you take some of the amino acids in more concentrated solutions, you do get absorption bands at 3650 Å where they are not normally present in dilute solutions. In other words, what one is suggesting is that it is the interaction which is essentially producing this energy gap. It is not the ordinary if you like, molecular absorption bands due to normal rotation or ibration of the molecules, it is the system formed by hydrogen bonding to form complete conjugated system and this is not normally present in most amino acids. But if they are interacting you will get this extra band turning up.

Prof Theorell Yes, this is clear to me, but I don t quite agree. Of course, you could perhaps do something with 3-amino acids like tryptophane but you cannot make tryptophane in one protein molecule close together by concentrating the solution. I hav seen such Koller effects as you have shown sometimes but have never seen it happen with colourless protein and I don t believe that absorption bands will go ery much higher than the ordinary ones. A little absorption is always present but it is terribly little unless you have some impurity present.



Fig. 12



Fig. 13

Figure 11 shows a cancer obtained in rabbits. We started the experiment, reported with Dr Graham and Miss Croninger with 48 rabbits that received about 150 mg of smoke condensate 5 times a week for 6 years. At the end of 3 years all of the rabbits had developed cancer Those of you who are pathologists know that it is not too easy to develop carcinomas in rabbit ears, the tissue being much more resistant than that of mice.

Figure 12 shows another cancer having eaten through the ear There is doubt sometimes among pathologists as to whether these tumours are carcinomatoids or really invasive cancer There can be no question about the first one, having metastasized to the ear The second cancer as shown in Figure 13 has spread to the thoracic organs. We therefore have shown that tobacco smoke condensate is carcinogenic to mice and rabbits. Prof Druckrey showed yesterday that it is carcinogenic to rats and Blacklock has also shown that if he took cigarette smoke condensate together with tubercular bacilli and injected into the hilum of rats he was able to produce cancer also in that region. In other words the substance that we believe does produce cancer in man, has been proven to produce cancer in mice rabbits and rats.

Laboratory Contributions to the Tobacco Cancer Problem

Dr Ernest L. Wynder
Sloan Kettering Institute for Cancer Research, New York, USA

It is a particular pleasure for me to participate in this symposium because, some eight years ago I first visited Stockholm, to work with Prof Ahlbom trying to determine the causes of Plummer Vinson's disease There was something in this study which I think applies to the discussion of yesterday and today These studies showed that some dietary deficiencies contribute to the development of Plummer Vinson's disease and subsequently to cancer of the oral cavity and upper esophagus. When I first came to Stockholm, this disease was quite common. After the war nutritional changes were made in the over-all diet of the Swedish population and the bread was fortified with iron and vitamins. Today I am told by Dr Hultberg that Plummer Vinson's disease has become relatively rare In other words in a span of only ten years, a disease which was quite common has become rare, because I believe the nutritional intake of the Swedish population has changed. What does this prove in relation to our discussion today It proves that we are able to prevent a disease without necessarily understanding its cause or its pathogenesis. In other words, preventive medicine can be successful without completely understanding the causation of a given disease It has thus been successful in Plummer Vinson disease it has in the past been successful in cholera and many other communicable diseases, and I am sure it can also be successful in our prevention of certain types of cancer

Before going into the laboratory contributions in the tobacco cancer field, I would like to present a few statistical and epidemiological data which show that smoking is in fact a cause of cancer of the lung. Because, if it were not for these data, I doubt whether many of us would spend so much time on laboratory studies. The laboratory studies have their main significance because of the human data already at hand. The basic proof that smoking is a cause of lung cancer is statistical and epidemiological. It is unfortunate, that, at least in the U.S., the term "statistics" has often been misused and that there is a general feeling that you can lie with statistics. I think we physicians have contributed to this concept, because we have not handled statistics properly Often it has been physicians and surgeons who presented statistics in such a way as to let their results look better than someone else's. There is a well-known story which I am sure you may have heard, where a physician reports the success of a new drug on monkeys and reports that 33 per cent of the monkeys upon receiving this drug were improved, that 33 per cent of the monkeys did not get better and

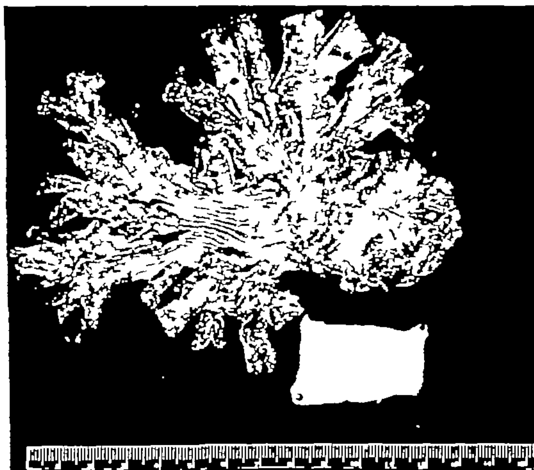


Fig 15

stated. is in agreement with the human data.

There are some preventive aspects that you can deduce from these laboratory ex periments which ha e a bearing on the human problem.

Figure 16 shows a study which we have done on the dose response of different amounts of smoke condensate to the production of skin cancer in mice You will note that, f we applied to the mouse 5 g or less per year of tobacco smoke condensate we were not able to produce any can cers. This of ourse explains the fail re of Dr Passey to repeat our work. But it clearly shows that tobacco smoke conden sate is not a very strong carcinogen. This is of course lucky for us because if it were a very strong carcinogen probably most of the smokers would succumb to cancer of the lung But in most environmental car cinogens we really only deal with weak carcinogens. Weak as it may be, it ac counts for nearly 30,000 American lives per year But, this dose response must be kept in mind.

Figure 17 again on the same subject. shows that if we applied tobacco smoke

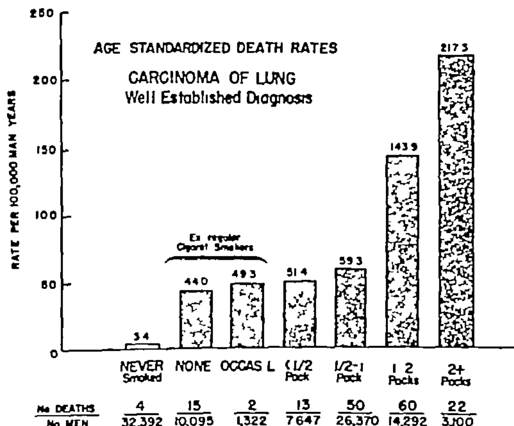


Fig. 2

study. It shows that British physicians who smoked heavily have a much higher risk of developing cancer of the lung than those who did not. It shows that those of us who are physicians or scientists are just as liable to this disease as the lay population.

We carried out a study in which we compared the smoking habits of the American male and female populations. This study shows, in agreement with Haenszel and Shimkin, that the present ratio of cancer of the lung is entirely in agreement with the long-term smoking habits of the two sexes. You will note that if air pollution were a major cause of lung cancer then the ratio ought to be more similar because women are exposed to the air as much as men. On the other hand, we found that women who do develop lung cancer smoke far more excessively than the control population.

Some critics, in evaluating these data may say "We agree there is a major statistical difference in smoking habits between lung cancer and control groups, but this does not mean causation. There may be a constitutional factor that makes one smoke and that also gives one cancer of the lung. Fisher took the same point of view and stated that there may be some genotype responsible for this. It has to be a very interesting genotype, I believe, be



Fig. 18

ready smoked for more than 40 years before giving it up. As you know it is a very unfortunate incident of history that Dr Graham, who has contributed so much to knowledge of the surgery and etiology of lung cancer was to succumb himself to this disease.

Figure 18 shows that upon inhalation a great deal of smoke condensate is retained in the lung. We find that 90 per cent of the smoke condensate upon deep inhalation is retained by the lung in contrast to only 10 per cent if you only take the smoke *into you mouth.*

Figure 19 shows the relationship of the amount of smoke condensate to butt lengths. We have shown that the second half of the cigarette contains up to 45 per cent more tar and nicotine than the first half. It is for that reason I have been very

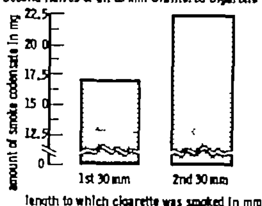


Fig. 19

much interested in this ring that the Swedish Tobacco Monopoly is putting on king size cigarettes. We are certainly in agree-

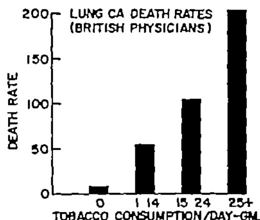


Fig 4

Seventh Day Adventists was 90 per cent less than in the general population. Now if the constitutional theory or the genotype theory is correct, we now have to argue that this genotype must make you smoke cigarettes, must cause cancer of the lung and must prevent you from joining the Seventh Day Adventist Church.

This is n summary the epidemiological evidence – that smoking is, in fact, one of the causes of cancer of the lung Whether you call it causative or whether you call it contributory associated or related it really makes no difference. The fact is, in the absence of smoking and particularly cigarette smoking cancer of the lung is a rare disease In iew of the fact that in the U.S. and England, and many other western countries, cancer of the lung today is the most common cause of cancer death in males we must gi e this problem ou fullest attention. It is precisely for this reason that th laboratory studies, which I will review for you now are so important.

The laboratory studies in my opinion cannot prove that a given factor causes cancer n man. Their main val e lies in supporting human evidence and in providing an explanation of the mechanism of carcinogenesis in a particular instance. There are some groups in the U.S who take a more radical point of view and they believe that any time that you produce cancer in an experimental animal, this substance must be suspected to produce cancer in man. I do not know whether the cranberry scare that was raised last Thanksgiving in the U.S was discussed in the Swedish newspapers. But here based on a single animal experiment, The Food and Drug Administration took the position that any cranberry contaminated with aminotriazol had to be taken off the Amer ican market. Certainly if we take this radical iew on cranberries, how can one fail not to take the same radical iew on smoking? I do not share this particular view— I believe what is really needed is a combination of human and animal evidence. On the other hand of course if a substance produces cancer in animals and it is not absolutely necessary that man use thi substance then of course we should avoid it.

This is the epidemiological data available up to date. Figure 6 shows you the smoking machine currently in use at my institute A smoking machine prepared by Cigarette Components Ltd. in England—it is a ery fine working model and tries to simulate human smoking habits as closely as possible. When we do tar determinations we use the electrostatic procedure. For chemical determinations cold traps are used. In addition, for larger tar determination, we have a distant cousin of this machine which smokes 100 cigarettes at a time In our laboratories we smoke about 1 million cigarettes a year which may be one of the reasons why tobacco consumption is going up in the U.S

Figure 7 shows the way smok conden sate looks in a glass tube. Sometimes when you speak to members of the tobacco in-

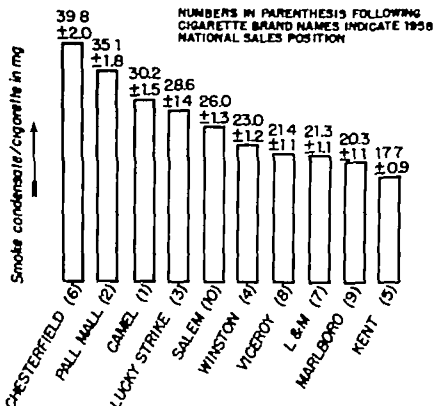
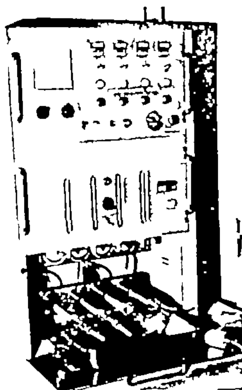


Fig. 1

the activity is in the acidic and neutral portions but you will note that there is very minimal activity in the nicotine-free basic portion Then as we separate the neutral tar from the acidic tar a little activity remains in the acidic tar But then I think we were very lucky to find that upon fractionating the neutral tar nearly all of the activity came out in that fraction eluted with carbon tetrachloride We judged from this study that though the major activity lies in the neutral portion, additional activity lies in other portions, which means that the other portions either have other carcinogens or perhaps some type of promoting substances.

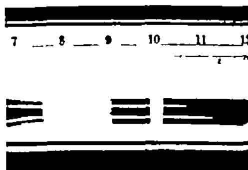


Figur 6

being smoking one or two cigarettes a day without inhaling it. His risk of developing lung cancer would certainly also not be greater than that of a non-smoker Since this time, Engelbreth Holm in Denmark, Orris at New York University Bock at Roswell Park, B ffalo and Sugiura at the Sloan-Kettering Institute ha e also been able to obtain cancer in the experimental animal

These tumours can also be obtained with cigar ta and with pipe tar in roughly the same yield as with cigarette tar (Figure 10) If you take an all tobacco cigarette, your yield is slightly less probably due to the fact that this cigarette burns differently than a normal cigarette does, producing probably some chemical differ ences in the tar constituents which we have not analyzed so far Anyway cigar tar and pipe tar are at least equally carcinogenic to mice as is cigarette tar

weak carcinogen to begin with, if you di lute its concentration too markedly it is no wonder that you do not obtain any cancer It would be just like a human



F gur 7



F gur 8

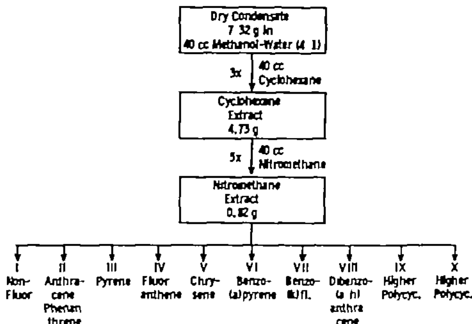


Figure 25

ULTRAVIOLET ABSORPTIONS SPECTRA

SPECTRAL RANGE: 415 220 mμ
SOLVENT: CYCLOHEXANE
CELL LENGTH: 5.0 cm
OPTICAL DENSITY 0.0 – 1.0

I 3,4-BENZPYRENE CONCENTRATION: 387 μg/L

II UNKNOWN ISOLATED FROM TOBACCO SMOKE CONDENSATE

250 300 350 400

II
I

Figure 26



Figure 11

HIGHER POLYCYCLIC AROMATIC HYDROCARBONS ISOLATED FROM CIGARETTE SMOKE CONDENSATE

Polycyclic Hydrocarbon	Relative Carcinogenic Activity	From Fraction	ppm
Benzo(a)pyrene (3 4-benzpyrene)	+++	7	0 7 (1 2* 0.1)
Dibenzo(a, h)anthracene (1 2.5 6-dibenzanthracene)	+	8,9	0 1 0 15
Benzo(b)fluoranthene (3 4 benzfluoranthene)	++	7	0 1
Benzo(j)fluoranthene (10.11-benzfluoranthene)	++	7	0 15 0 2
Benzo(a) anthracene (1 2-benzanthracene)	+	6	0 1
Chrysene		6,7	1 5 2.0
Benzo(e)pyrene (1 2-benzpyrene)	±	7	0.1
Benzo(g, h, i)perylene (1.12-benzperylene)		7 8	0.15 0.2
Benzo(k) fluoranthene (11 12-benzfluoranthene)	±	7 8	0 15 0 25
Alkylchrysene	?	6,7	1 5 2.0
Alkylfluoranthene	?	5 6	1 5 2.0
Alkylpyrene	?	4,5	2.0 2.5
Benz(mno)fluoranthene		6	0.1
Fluoranthene		4,5	2.5 3.5
Perylene		7	0.1
Pyrene		3 4	2.5 3.5
11 H-benzo(b)fluoranthene (2,3-benzfluoranthene)		5 6	0.5

Average from three analysis
** Calculated by the tracer method.

Relative carcinogenic activity to mouse skin

	high	±	very weak
	moderate	?	not yet tested
	weak		inactive

Fig. 29



F gu 14

Now again, t has been said. Well, cer tainly you produce cancer in animals but th doses that you use are so enormous that no human being would ever smoke that many cigarettes We investigated this question just to find out exactly what the dose relationship is and th following figures may be of some interest to you in this regard.

Figure 14 shows a human lung that we dissected in our laboratory As you know more than 50 per cent of all human lung cancers occur in the major bronchial tree which is dissected out a shown in Figure 15 What interested us was to find the relationship of surface area of the human bronchial tree to the average mouse skin. The picture shows a human bronchial tree opened up and compared in size to an average mouse skin. It is about 6 times larger But, whereas we applied 10 g per year to the mouse skin, the a erage l ng cancer patient is exposed to more than 300 g of tobacco smoke condensate per year So, you see we are well within the confines of the amount of smoke conden sate we apply to the mouse So much about the biological evidence which, as I

Potentiometer Graphs

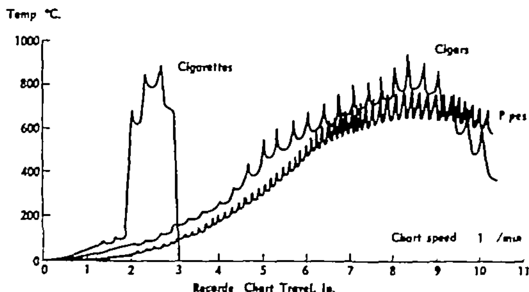


Figure 31

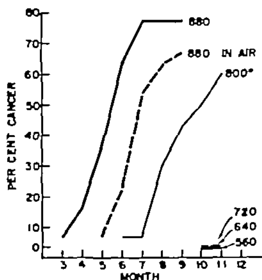


Figure 32

the 3 4-benzpyrene value which are not significant from one value to the next, but which are just significant if you go from 1 to 3 puff a minute. The sidestream of the smoke has a very marked increase in 3 4-benzpyrene. This is what we could have expected because it appears that the polycyclic hydrocarbons are a result of incomplete combustion of the tobacco as exists in the glimming zone and that during the actual puffing of the cigarette some polycyclic hydrocarbons are destroyed.

We studied the 3 4-benzpyrene content of the first half of the cigarette and of the second half We got a surprise because we expected that the second half of the cigarette would contain more 3 4-benzpyrene than the first half because of repyrolysis

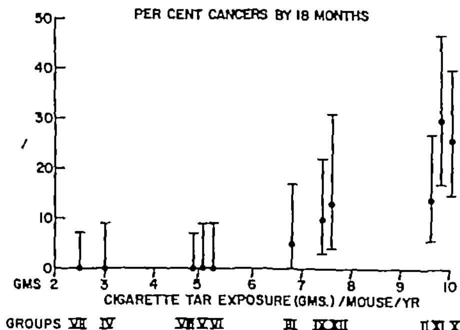


Fig 16

condensat to an animal for a certain period of time and then stopped its application, the tumour yield was markedly decreased. If we ga e the animals tobacco smoke condensate for only six months and then stopped, we noted a few papillomas which then regressed. Up to 12 months we got an increase in yield, and after 12 months the yield was not increased further This is in line w th a question very often asked by patients who say "But Doctor I ve already smoked for 30 or 40 years and it may well be too late to give up smoking It is always ery difficult to interpolate exactly from animal to human data, but, if you can do so, t suggests that if you have smoked for 20 years or less and give up smoking your risk is markedly reduced if you have smoked for 40 years or more probably the changes are irreversible. I recall a ery unfortunate example n this regard because as Dr Graham and I went through this type of reasoning some years ago he had al

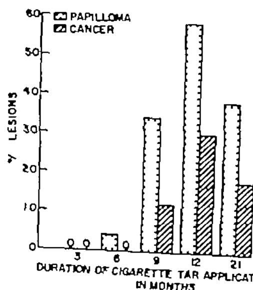
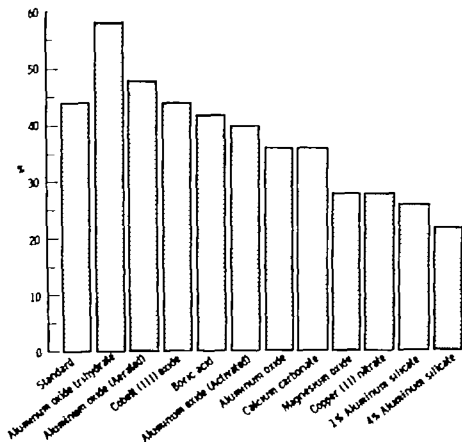


Fig 17



Figu 35

tested. In this experiment alone, therefore, we smoked 650 000 cigarettes.

Figure 35 shows the biological results of this study With the exception of copper nitrate and aluminum silicate, the reduction was not marked, and even in these instances I am not sure that the reduction is really biologically significant.

We were disappointed because we had suspected that some of these catalysts ought to gi e a biological reduction because among other things, we had gotten a 20 per cent tar reduction w th some of these catalysts even with as little as 5 per cent of the additive. By luck, we had in two instances used another smoking machine which smoked onl once a minute In the previous case we have used our standard smoking machine which smokes three times a minute the reason we chose this machine is the great amount of tar to be obtained and also because we had previously shown that comparing the biological activity of a standard tar smoked three times a minute to once a minute showed no difference

Figure 36 shows the biological activity of tar from cigarettes, smoked once a mi nute to which calcium carbonate and copper nitrate had been added. The standard tar has the same activity as the standard tar smoked three times a minute Cigarettes smoked once a minute with calc um carbonate and particularly w th

ment that it would be advisable to throw the cigarette away when you are half way through – this may well be the only recommendation the American tobacco industry will readily accept!

This may be one of the explanations why there is so much more lung cancer in Great Britain than in the United States, because whereas the average butt lengths of the American smoker is 30 mm the average butt length of the British smoker is only 18 mm.

Another example in respect to tar content is shown in Figure 20 which shows that the more frequently you puff on the

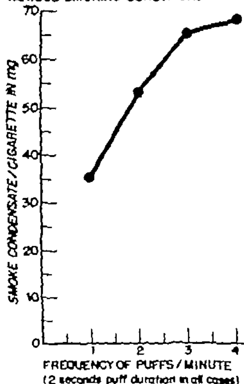


Figure 20.

cigarette the more smoke condensate you obviously get. The average smoker is believed to puff only once a minute.

Figure 21 shows the yields of the leading ten American cigarettes which together constitute 85 per cent of the total cigarette consumption in the U.S. You will not a very marked difference between the non-filter cigarettes and the filter cigarettes. There has been a great increase in the U.S. in the use of filter cigarettes which today make up 50 per cent of the total cigarette sales.

You will note that the filter cigarette with the least tar content of 17.7 mg has only half the tar content of the cigarette with the largest amount of tar 39.8 mg. In clinical studies we have shown that in smokers who shift from a non-filter to an effective filter cigarette, 50 per cent of those who do have symptoms, primarily cough, the cough improves and mostly disappears. We feel that if you must smoke an effective filter cigarette is one of the ways of giving you some protection. But by no means is the filter cigarette safe.

So much about biological studies and dose studies. Now a word about chemical studies which are in my laboratory under the direction of Dr Dietrich Hoffmann. The chemical data that I am now presenting to you have been carried out under his direction.

Figure 22 shows a study reported in 1957 with Dr George Wright where we broke down the total cigarette smoke condensate in an attempt to find the important carcinogenic fractions. All of these materials were applied in 50 per cent concentration to at least 30 animals with the exception of the eluates of the neutral tar which were applied in 10 per cent acetone solution to the experimental animal. The plus signs underneath each group indicate the relative biological activity. You will note that as we fractionate down, most of



Figure 38

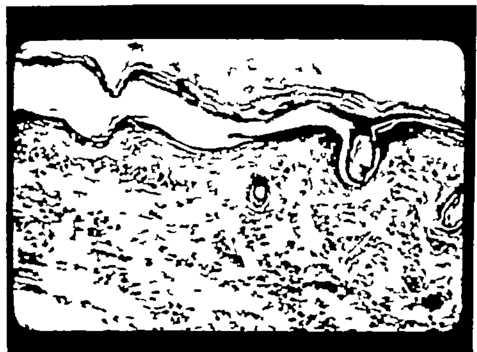


Figure 39

CIGARETTE TAR FRACTIONATION - RELATIVE BIOLOGICAL ACTIVITY

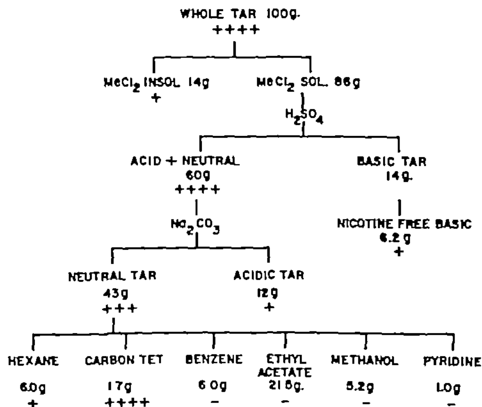
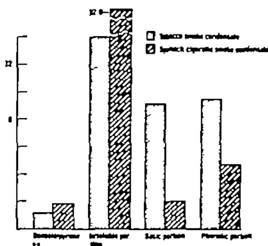


Figure 2

cent concentrations, employing in one set of experiments DMBA as an initiator and in another set 3 4-benzpyrene.

Figure 41 shows a mouse after using DMBA as an initiator and phenol as a promotor with multiple tumour formation.

Figure 42 shows an experiment we have done with spinach. This experiment was not done in an attempt to find a substitute for tobacco Spinach has other values and we would certainly rather eat it than smoke it. It was done to tell whether other



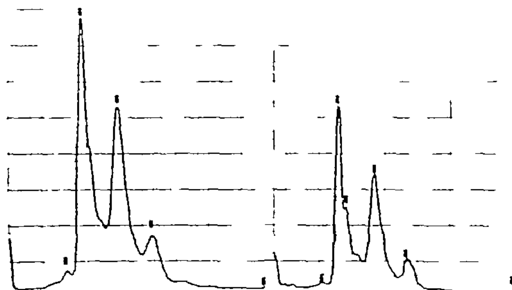
Figu 4



F gu 41

organic material would also form polycyc lic hydrocarbons and some of the other fractions that we can find in cigarette smoke condensate We found that spinach does not really make good cigarettes it doesn t burn as well as tobacco. You will note that spinach condensate has more 3 4-benzpyrene than cigarette smoke condensate. This may be due to the fact that the spinach cigarette did not smoke very well. We found that the temperature was fluctuating, and that a maximum tempe rature of only 750 was reached.

In a short-term test using spinach tar comparing it to tobacco tar we noted to our great surprise that the cigarette tar was far more active than the spinach tar This, of course, has its explanation. We found not only a marked reduction in the basic portion which we of course expected, but a 50 per cent reduction in the phenolic portion. This is in line with our concept that the phenolic portion plays a very important role in the promoting activity and the irritati e activity that cigarette smoke condensate has. Therefore this spinach experiment not only told us some



F g 7

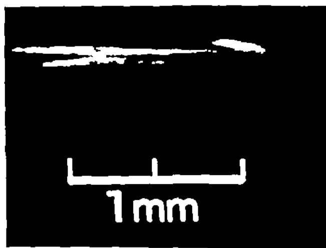


Fig 28

Figure 29 shows the polycyclic hydrocarbons that w have identified in tobacco smoke condensate at least eight of which are carcinogenic in pure form. We have stated repeatedly that the polycyclic hydrocarbons by themselves can account for

production of cancer are a combination of initiating carcinogens and promotors among which the phenols are probably the most important ones.

But there also must be promotors in the acidic fraction and in the basic fraction and even in the carbon tetrachloride eluate of the neutral tar In the latter case they may be unsaturated aliphatic hydrocar bons. Our work in the chemical labora tory is now directed towards further defining the promoting substances.

We have summarized statistical reasons as to why we believe that smoking is a major cause of lung cancer and we have outlined to you the experiments conducted in the biological and chemical laboratory designed not to prove that smoking is a cause of cancer of the lung but to deter mine the mechanism of this relationship and to show ways in which we can reduce the carcinogenic effect of tobacco smoke condensate.

In conclusion, we should like to recommend the following preventive measures.

1. If we can possibly do so we should try to give up smoking But this, as I gather at least among my own friends in New York, is most difficult indeed because even though we are most convinced by these data, we always believe it will never happen to us but it will happen to the other fellow So I don t think we can make very much head way on this. I do believe however that the youth of our countries is much more susceptible to this type of data than our adult population if w present the data to them correctl

2. Those of us who cannot giv up smok ing bould try to moke less. And w should try t moke the most effective filter cigarettes a ailable Tar reduc tion in cig rette cannot only be obtained through an effective filter but can also be obtained by choosing tobacco types which are low in tar content and through high porosity paper Our tests show that high porosity paper has not contributed to dif ferences in the combustion products of a cigarette but it can contribute to tar reduction. In other words, if we must smoke, smoke a cigarette which is as low in smoke condensate and in nicotine as possible. We should not try to inhale because upon deep inhalation, 90 per cent of the smoke condensate is retained if we hold the smoke only in the mouth only 10 per cent is absorbed. Finally we should not smoke to the very butt. These steps will all lead to a reduction of our exposure to tobacco smoke condensate.

3. Studies must be continued in the field of precursors. We have previously re ported the fact that we believe that the precursors cannot be so altered as to reduce the polycyclic hydrocarbons. We have found that, for instance after we washed cigarettes in hexane the resulting cigarettes ha e just as much 3 4-benzpyrene as the standard ciga rette. We believe that nearly all orga nic material, as Landsey has also shown, when pyrolyzed will form poly cyclic hydrocarbons. On the other hand, it is possible that the precursors to such substances as the phenols may be more readily changed. For instance we find a ariance in the polyphenols which we regard as precursors to the phenols in aircured and flue-cured tobacco. We are currently undertaking studies to find out what, in fact, is the polyphenol content of air-cured and flue-cured tobaccos and whether cigarettes made of these tobaccos might differ in the content and mak

not more than 3 per cent of the total biological activity of tobacco smoke condensate and that even the carbon tetrachloride fraction of the neutral tar contains only enough polycyclic hydrocarbons to account for 10 per cent of its total activity So we were certain that other initiating carcinogens or promoting substances have to be present. However we regard the polycyclic hydrocarbons as initiating carcinogens in the absence of which the activity of tobacco smoke condensate would be markedly reduced. We have I believe given proof to this concept in an experiment where we ha e removed the carbon tetrachloride fraction from tobacco smok condensate and recombined the rest of the condensate. At the end of 15 months, when we ha e normally already about 30–40 per cent tumours, and 10–20 per cent cancers, we have only 3 papillomas in these animals. The question of course may be raised whether recombination of tobacco fractions might reduce the activity but in a previous experiment where we separated acidic, neutral and basic portions of tar and then recombined them, we ha e shown that no activ ty was lost in such separations.

In our search for other carcinogens, we suspected that benzfluoranthene might be carcinogenic on the basis of its structure and we have shown that benzo(b)flouranthene and benzo (j) fluoranthene are active even in 0 1 per cent concentration (Figure 30) M n, *o-benzfluoranthene was not* found to be active. Upon finding that these polycyclic hydrocarbons were active and probably played an important role in tobacco carcinogenesis, we were interested to learn someting about the mechanism of the formation of these materials.

Figure 31 presents a study by Touey and Mumpower Showing the peak temperatures of cigarettes, cigars and pipes. The peak temperature of the cigarette that

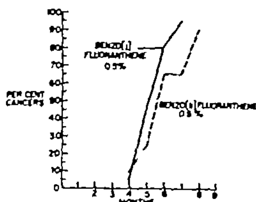


Fig 30

is being puffed in about 884 C. At rest, that is without puffing it is 835 C. The peak temperature of the cigar is slightly higher that of the pipe is lower but the plateau of the cigar and pipe temperature is much wider We regard the formation of polycyclic hydrocarbons as a result not only of peak temperature but of the duration at which the temperatures are maintained.

To study this point further we pyrolysed a tobacco extract obtained by washing tobacco with hexane at these various temperatures (Figure 32) By the end of 10 months we found no activity in the pyrolysate at these temperatures whereas there was marked activity at 880° either in the absence of air or with air Later on we got *additional* tumours with *720* and 640° but it certainly shows that the activity is markedly reduced as you reduce the temperature. So the temperature certainly has a great deal to do with the formation of carcinogenic substances.

Figure 33 shows a further attempt to study the formation of 3 4-benzpyrene and perhaps other polycyclic hydrocarbons. As the puff rate was increased to 2 or 3 times per minute w get minimal increases in

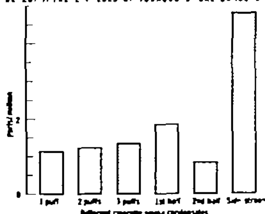
in the U.S. I think this is probably true. Several studies have shown that there is a relationship of smoking not only to cancer of the lung, but also to the occurrence of myocardial infarction. If smoking is a factor both in myocardial infarction and in cancer of the lung and since it is true that myocardial infarction is much more common in the U.S. than in England, the competitive risk factor would be more important in the U.S. than in England. In other words, if you die of myocardial infarction at the age of 45 you obviously cannot die of lung cancer at the age of 50. I think that the greater prevalence of myocardial infarction in the United States and its relation to smoking may be another reason why lung cancer is somewhat more common in Great Britain.

3) Another point that we have considered and that we are studying now — We are comparing the more common cigarettes in Great Britain with those in the U.S. We have found several variations, for instance that the British cigarette is more fully packed. I do not know whether this has a bearing upon the smoke constituents of the British cigarette. We have found that a different type of tobacco is used. The British use largely Virginia tobacco whereas we use a great deal of Burley, Maryland and other tobaccos, and this has to be investigated. There are several other factors that remain to be investigated. There is also a difference in the use of air-cured and flue-cured tobaccos in the British and American cigarettes, which have different amounts of polyphenols, as I have indicated before, and this also remains to be investigated. So there are several interesting data to be studied largely in the make-up of the British cigarettes compared with American cigarettes. Then the epidemiological findings can, I believe, at least in part, be explained through these differences.

Prof. Druckrey: First, may I make a short remark about the question regarding the different frequency of lung cancer in different countries. In connection with this I have had extensive talks with our Japanese colleagues. The Japanese smoke very many cigarettes and start smoking already in their early youth. But in spite of this the frequency of lung cancer is not so very high in Japan. Our Japanese colleagues told me that this is due to the fact that the humidity of the tobacco, as well as that of the air is very high in Japan. So this may be a factor. On the other hand, I am very cautious when considering statistical results. And I think all of us are and we should be very critical on this point because the first law of statistics tell us that comparisons are allowed only between such factors that are really comparable and I think that this law has not always been respected sufficiently in discussing the connection between cigarette smoking and lung cancer. Cigarette smoking cannot be considered as a whole. For instance, the use of filter cigarettes or plain cigarettes makes a difference and is not comparable. Another very important point is, I think, that of inhaling. Dr. Wynder and myself are in complete agreement that inhaling or not is, indeed, a very essential factor. It may be very difficult to get clear statistical evidence as to the frequency of inhaling. Personally I try to get information on this point by asking different persons whom I know very well if they inhale or not. After having observed these persons and their smoking habits for a certain time I can say that there are many persons who pretend to be non-inhalers but of whom I know from my own observation that they do inhale. So, it is very difficult to get clear information in a statistical survey. I made one observation, however, and I should like to ask Dr. Wynder about this because I think he has mentioned a similar observation in his paper in the New England Journal of Medicine. This observation is that people who smoke filter cigarettes do not inhale as frequently as people who smoke plain cigarettes. I may be mistaken, but I do have this impression. On the other hand, Dr. Wynder said that filter cigarettes are by no means safe cigarettes. I do not consider filters to be the solution to this problem. If one measures the amount of tar produced by plain cigarettes and by filter cigarettes one *may find a difference in the order of 20—30* per cent or perhaps 35 per cent. But if the calculation is based on direct extraction of the tar from the filters, then the effect of the filters becomes much lower. So, the results depend to a high degree on the technique used for the determination of filter efficiency, a fact that has often been used purposely. This means that we have to be very cautious and critical in using the results that are presented to us.

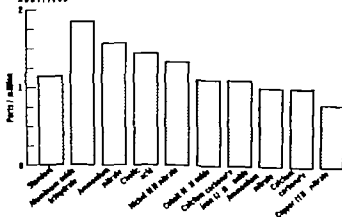
Now if I may come to the question of spinach. You used spinach as a control. It was very interesting to see and learn that the benzpyrene content of spinach smoke was much higher than

of alreadv condensed cigarette smoke condensate. Kotin and Falk had already reported that the second half contained more than the first half So when Dr Hoffmann first found the result we thought we must ha e made an error — so we repeated it and we got precisely the same value Dr Laskowski in Chicago repeated t also and also found that the first half contained twice as much benzpyrene as the second half An explanation of this is a good deal more difficult than if it had been the reverse. A possible explana tion would be that the smoke condensate that settles in the second half of a cigarette may in some way have acted as a catalyst. We have been previously interest ed in catalysts with the hope that we could find a substance which would either alter the temperature of the cigarette which would make the combustion more complete or perhaps bring more oxygen to the reaction.



Figur 33

Figure 34 shows an attempt with various additives to test first 3 4-benzpyrene values and later biological activity When I stress that we used 3 4 benzpyrene values, I mean that we are using 3 4-benz pyrene as one of the indicators. In general it seems easier to increase the benzpyrene value than to decrease it. In fact there was only one material where we had some reduction and that was copper nitrate which is in agreement with results publish ed by Bentley In all of these experiments we added from 4 to 5 per cent of the additive to cigarette tobacco. In each instance this was added to 50,000 cigarettes which were chemically and biologically



F gur 34

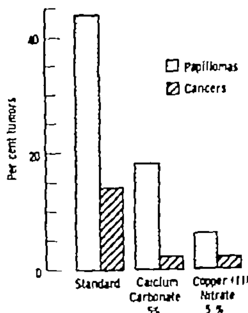
not remov any condensate particle selectively. The filter therefore is only justified if it actually reduces the amount of exposure to the smoker. We have, so far not observed that the filter smokers in our country inhale less. W are doing study on it t the moment so far it ppears to us that they inhale as much. I fact, nearly all, or more than 90 per cent, of the American cigarette smokers do inhale.

In respect t your question on the benzpyrene content of spinach.—I believe of course that this is produced in the combustion process. I fact, most organic materials, as Lindsey has shown, whether you burn suga cellulose or paper will produce polycyclic hydrocarbons. W belies that these are formed during incomplete combustion. I think your question as to what the catalysts do was whether they detoxify or how else they change th combustion process in such way as to lead to more complete combustion. This, of course, remains to be studied on the basis of chemical analysis of all these tars obtained from the various additi e cigarettes. If, indeed, we find that t is the phenolic fraction which is primarily reduced, then our conclusion might be different from that when we find that th polycyclic hydrocarbon fraction is reduced. The determination of these findings has to wait for the complete chemical analysis of these st dies M y I sa that we regard the additiv study as important and that, pon finding that the once-a-min t tars of the calcium carbonat and the copper nitrate cigarettes are so reduced, we are now repeating the once -minut stuff with five additives that w think are most promising, using 100 mice on each. And we think that these findings may be so important that we are smoking 4 hours day so that w can get the animal experiments started. And they should have been tarted about week ago.

I respect t your question on initiators and promotors, t is, of course true that initiation and promotion can perhaps be somewhat more readily studied on the skin than subcutaneously. I would be ery in erested, though to see what would happen if you would giv to your rats, let us say 3 4-benzpyrene very minute doses as you hav already given and if you could giv them phenol or phenolic fraction t the same time. Of course one of th surprising f tures about initiating carcinogen t least in the skin as I said before is that they can be activ in ery minute concentrations. As far as the concentration of the phenolic fraction is concerned, in our own study we re doing t in 10 per cent concentration as well as in .5. It is present in tobacco smoke condensate in about 10 per cent concentration.

The positiv results already published by Roe wer obtained with about 18 per cent concentration. So it is roughly in th range i which th phenolic fraction is present in tobacco smoke condensate. At the moment w are making dilution studies with the phenolic fraction and we find that on the short term test they are quite positive. Indeed, in 10 per cent concentration. W do not believe that we can find just one promoting substance or just on initiating carcinogen. After all, we have ery complex product here. W believe that there are probably many other initiating carcinogens, th nature of which we do not know. W hav made one study in which we have pyrolyzed tobacco extract and we have found some fractions which came off the column very late after benzpyrene and which contain onl unknowns and are very highly activ to the skin. So we certainly believe that there are other initiating carcinogens. Similarly there are certainly other promoting substances than those i th phenolic fraction. I would therefore never expect that, i the concentration as present in the tobacco smok condensate, w would be able to show that it alone in that concentration, would be promoting or initiating to th animal. After all, the effect of tobacco smoke condensat is summation of all the initiating and all the promoting substances, nd all we can hope for is to find the major ones which pon removal may giv reduced activity.

Prof. Klein: One argument one often hears when discussing the statistical studies on lung cancer and smoking is that while these studies establish that there is a relationship between these two phenomena, this relationship is not necessarily causal. One then must ask the question "What other relationships ould there be biologically?" I think Sir Ronald Fisher list three. H says that when you find correlation between A and B, and he does not doubt that there is such correlation between smoking and lung cancer then it is either A that causes B or B that causes A or both A and B re caused by C. Now what does this mean biologically. One is that smoking causes lung cancer. The other is that people who hav precancerous condition in their lungs or in their trachea are more liable to start smoking than people who do not ha such precancerous condition. This is that B causes A, but I think that Si Ronald Fisher dismisses this as improbable and that



Figur 36

copper nitrate showed a very marked reduction in biological activity. This reduction in activity is also indicated in that the first papilloma appeared much later than in the standard cigarette. The reason why we got a difference here whereas we got no such difference when smoking three times a minut may be that when one smokes three times a minut one may overload any catalytic action that an additive might have. In view of this, we are now repeating these studies with our most promising additives in the once-a-minute smoking machine. If we find again a marked biological reduction with some other additives which are more practical than copper nitrate, we may have one way of effectively and practically reducing the biological activity. We are particularly interested in calcium carbonate and iron oxide, which together may be a practical and effective catalyst. These studies are now in progress. I believe that the effect of these materials is not due to the rather minute reduction for benzpyrene but probably to reduction in other components which we are investigating at the moment. For instance we found that in the copper nitrate condensate we had a reduction of 50 per cent in the phenolic fraction which may be the most important reduction as far as its biological action is concerned. We are trying to find out now not only how we can reduce 3,4-benzpyrene and polycyclic hydrocarbons, but also how we can reduce possible other initiating carcinogens or promoting substances. It is the promoting substances that we are concentrating on at the moment.

Figure 37 shows short term tests, sebaceous gland tests, done with cigarette tar the acidic portion, neutral portion, basic portion phenolic portion and the cigarette tar minus the phenolic portion. When we first reported the short-term test, some workers thought that this short term test was positive because of the polycyclic hydrocarbons present in tobacco smoke condensate. It was clear that the polycyclic hydrocarbons could not be responsible for this because in pure form, 3,4-benzpyrene gives a positive short-term sebaceous gland test in only 1 part per 2,000 whereas there is only about one

SHORT TERM TESTS

Condensate Fractions (33%)	Relative Activity
Cigarette	+++
Acidic	++
Basic	
Neutral	
Phenolic	+++
Cig minus Phenol	+

Figur 37

A correlated Histological Cytological and Cytochemical Study of the Tracheobronchial Tree and Lungs of Mice Exposed to Cigarette Smoke

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This investigation was supported by a grant from the American Tobacco Industry Research Committee New York City New York, USA.

I INTRODUCTION

In recent years the question of a causal relationship between cigarette smoking and human lung cancer has become a widely discussed issue. Although statistical clinical and histopathological data on humans, as well as experimental observations on animals, have been interpreted by some investigators in favour of such a relationship the topic is still controversial, and additional research is urgently needed

The experimental approach to this problem is by no means an easy task, not only because our present-day knowledge of carcinogenesis in general is so scanty in other words, because we have so little information concerning factors and the pathways by which tumours are produced, but particularly because cigarette smoking is an exclusively human habit which has not been duplicated on a large scale in animals, although, for show purposes a few chimpanzees have been taught to smoke The most desirable experimental approach would certainly be if one could develop the smoking habit in anthropoid apes and then study under controlled conditions the sequence of events produced in the tracheobronchial tree of the animals. Needless to say the setting up of such a study as important as it would be is extremely difficult. Large numbers of anthropoid apes and proper housing facilities, which would be needed to permit studies over the whole life span of the animals, would involve considerable expense. Furthermore one would have to search for specially trained personnel able to handle the anthropoids and teach them to smoke Since with the facilities at our disposal such a project was out of the

part per million of 3 4-benzpyrene in ciga rette smoke condensate So we already knew that this result had to be due to other substances. This study shows that n 33 per cent concentration the most im portant short term acti ity is in the acidic fraction and particularly in the phenolic fraction we find that when we remove the phenolic fraction from the total ciga rette smoke condensate the activity on the sebaceous gland is markedly reduced.

Figure 38 shows the short term test of cigarette smoke condensate. You will note marked hyperplasia and destruction of the sebaceous gland.

Figure 39 shows the same test for the phenolic fraction. Again w not ery marked hyperplasia, even invagination, keratosis, and destruction of the sebaceous gland.

Figure 40 shows that after the phenolic fraction has been removed, we see prac tically no hyperplasia and complete presence of all sebaceous glands. This study suggests that the phenolic fraction may be a very important fraction accounting for the total biological activ ty Boutwell had previously shown that phenol in pure form in 10 and 5 per cent concentrations is an important promoting substance using DMBA as an initiator We have confirmed his findings and also shown that phenol is an important promot ng substance to dilute solutions of 3 4 benzpyrene. Roe, in England, has shown that there is a promoting activity of the phenolic fraction of tobacco smoke condensat using DMBA as an initiator We believe therefore that the phenolic fraction is an important promoting substance Our own studies are now only in the 3rd and 4th month. We are using the phenolic fraction the acidic fraction, the nicotine-free basic fraction and the neutral fraction in 10 and 25 per



Figure 40

The unique feature of this method lies not only in the possibility that, for example a DNA quantity as small as 2.5×10^{-9} mg can be determined in a single nucleus, but that this analysis can be done in microscopic sections *in situ*. In other words, since the architecture of the cells and their relationship within a tissue are preserved, a direct comparison between cell morphology and DNA content from cell to cell can be made directly under the microscope. Thus the DNA behavior can be explored under normal and abnormal conditions during such dynamic processes as growth, mitosis and meiosis.

The conventional biochemical analysis is obviously not suitable for the exploration of these problems, because the biochemical DNA determinations can be carried out only on relatively large cell populations and after the cells and tissues are destroyed and extracted. The DNA value, therefore, is, of course, only an average value. While such a computed average value may be representative for the cell if a cell suspension is analyzed in which each cell has the same uniform DNA content, it is actually an erroneous value if suspensions of cells with varying DNA content, such as is the case during cell division and, particularly, under abnormal conditions, are analyzed.

The possibility of a direct correlation between physiological stage of a cell, its microscopical appearance and its chemical composition assumes particular significance when one takes into consideration that in the final analysis, a change in physiological stage and morphology of a cell is more or less the expression of preceding chemical alterations. *The detection of intracellular changes in the DNA proteins before structural alterations manifest themselves is made demonstrable by the use of microspectrophotometry and interference microscopy* and, therefore we felt that a simultaneous study of morphological cell structure and of these important intracellular chemical constituents might help greatly in assessing the biological effect of cigarette smoke.

B. *Animal Experiments*

To carry out the investigation discussed in this report, an attempt was made to standardize as far as possible the conditions under which the experiments were conducted. The 600 mice which we used for this study were CF_1 female mice three months of age. Upon arrival, the mice were placed in cages located in a specially designed room which was used exclusively for these smoking experiments. To insure that the mice were exposed to smoke only when they were in the smoking chamber and that the control mice were not exposed to smoke at all, no smoking was allowed in this room. For each experimental mouse a control mouse of the same age and weight was used.

In order to study the effect of cigarette smoke, mice were exposed to smoke in a chamber which is shown in *Figure 1*. This apparatus permits the housing of both the exposed and the control mice at the same time under the same standardized conditions. The only exception is, of course, that the compartment containing the control mice receives no smoke while the compartment containing the experimental mice receives smoke from cigarettes mounted on a mechanism which lights them at required intervals.

Mice were exposed to cigarette smoke every day with the exception of weekends and holidays. If a mouse appeared sick, and especially if weight loss was noted, it obtained a rest from smoking. After the daily smoking period, the mice were taken

thing about the formation of polycyclic hydrocarbons but also erified our view on the phenolic portion.

Figure 43 repeats in somewhat greater detail our present concept of the way in which the total activity of cigarette smoke condensate must be evaluated and must be reported. In comparing the chemical constituents of different cigarett smoke condensates we should not only present the 3 4 benzpyrene values, which we are regarding onl) as one of the indicators of polycyclic hydrocarbon formation, but we must also present the acidic portion which w believe has promoting activity in line with ou own work and that of Holsti, who has shown that longchain fatty acids are promotors. We must further present the basic fraction in terms of total basic fraction and nicotine n iew of the fact that w ha e shown the nicotine

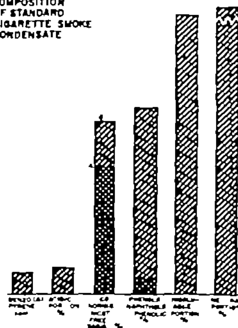


Fig 43

INITIATOR	PROMOTER ⟶ CANCER
Polycyclic Hydrocarbons	Phenols
+	
Unknowns	Unknowns (In Neutral Basic and Acidic Fractions)

Fig 44

free basic portion, at least in 50 per cent concentration, has also some promoting activity We certainly must present sepa rately the phenolic fraction and the phe nols because it has been shown that it has important promoting activity We must also present the neutral fraction. In other words, in the chemical evaluation and presentation of tobacco smoke condensate we have got to present all of these frac tions. We are now in the process of trying to identify other initiating or promoting substances, primarily in the acidic and n the phenolic portion. W believe that t is in this direction that the chemist, in coopera- tion with the experimental biologist, now must go.

Figure 44 shows our basic concept which can account for tobacco-induced cancer in the experimental animal a combination of initiator and promotor As I said already yesterday in the discussion to the layman it is rather surprising that an initiator in such minute concentration could be effective but, as has been repeat edly shown, DMBA even in a concentra tion of 1 microgram can act as an initiator in mice. There are many initiators present in tobacco smoke, not only 3 4-benzpyrene but, as, for instance, Klein has recently shown, 1:2:5:6-dibenzanthracene is also an important initiator The results of the

ental response, which was observed regardless of whether mice were exposed to cigarette smoke for a short or a long period, will be discussed later Suffice it to say here that the microscopic findings in the bronchi can be divided into *three groups no significant changes mild changes* and *severe changes*

There appears to be a stepwise sequence of lesions in the epithelium from a normal resting one to a swollen one to a proliferating one and finally to an atypical proliferating one

It should be mentioned that *the changes are often multifocal along the bronchi* and that, *although bronchitis was sometimes noted without proliferation of the epithelium there was never any proliferation of the epithelium without bronchitis*

Before demonstrating a few examples, the characteristic appearance of a bronchus from a nonexposed control mouse is shown in different magnifications in *Figures 3a 3b and 3c*

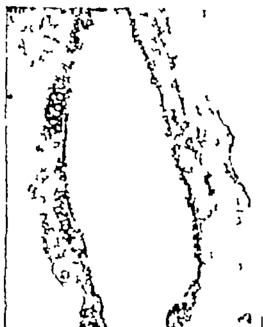


Fig 3



Fig 3b



Fig 3

up of the phenolic fraction. And finally experiments must be continued in the field of catal ts because we believe as already shown in the experiments out lined, that w th certain catalysts we can probably reduce the biological ac tivity of cigarett smoke condensate in the experimental animal.

As I said at the beginning the reason that I believe smoking is a cause of lung cancer is because of human data. We cer tainly do not know all the mechanisms that lead to cancer of the lung or lead to cancer in the experimental animal but we know certainly as much about this disease as we know about Plummer Vinson's disease and cholera. In other words, we are at a time when preventive measures can be introduced which will be successful be fore we know the final mechanism of this disease In iew of the fact that lung cancer represents uch a common cause of death in all of our populations and in view of the fact that we cannot readily cure lung cancer preventive measures are most important. I believe that the steps I ha e outlined and that cooperative meet ings such as this and the combining of ou efforts will lead to the eventual pre ention of cancer of the lung

DISCUSSION

Prof Caspersson May I ask, Dr Wynder what information is already available about the diff ren components in the phenolic fraction, chemical information, I mean

D Wynder W are just starting on the phenolic fraction now W hav first tried to devise good methods for determining the phenols themselves. The only thing I can say t the momen is that phenol itself is the most impor tant promoting substance. The phenols together account for about 9 per cent of the total phe nol fraction, but the precise amounts of the different phenols remain to be determined.

Dr Carruther W also hav been studying the phenolic fraction. So far w have isolated and identified by chemical methods seven phenols, including phenol itself and the three cresols all of which ha been shown to be promoting substances.

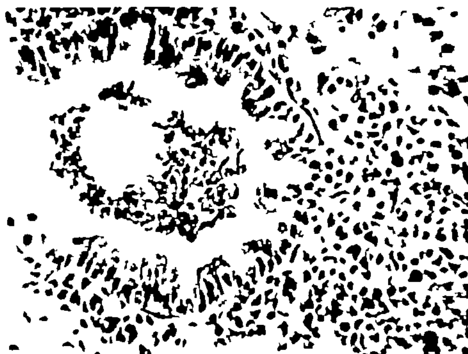
While I am here perhaps I might put few more questions to Dr Wynder My first concern is some of the statistical work. It is quite true that many of the retrospective and prospective studies show very close relationship between cigarette consumption and incidence of lung cancer But there still remain few things which do not em to fit in. One is Eastcott work in New Zealand Eastcott studied the lung cancer incidence in New England and compared the incidence between people who had lived in New Zealand all their lives and new immigrants from Britain who had arrived there within recent years. H found that, although the rates of smoking in the two groups seemed to be ery similar the incidence of lung cancer was higher in the people who had immigrated into New Zealand from England recently than it was in nativ -born New Zealanders. Very recently similar study with similar types of results has been made among white people in South Africa. Berkson in the United States also has persistently criticised the statistical correlation between cigarette smoking and lung cancer He points out that Hammond and Horn and also Dorn prospective studies show not only close correlation between cigarette consumption and lung cancer but also between cigarette consumption and ery large number of other diseases And he seems to think that there is something wrong with the statistical work. I would ery much like to know what Dr Wynder thinks of these points.

In another field, Paul Kotin in California accepts the statistical correlation but thinks that the effect of cigarette smoke is not mainly as source of carcinogens but as an irritant to the ciliated epithelium of the bronchial tree. He thinks that the cigarette smoke causes destruc tion of the ciliated epithelium and that the car cinogenic response is elicited by carcinogens which come from some other source perhaps

The gradual changes in the epithelium after exposure to cigarette smoke are demonstrated in *Figures 4a 4b 5 6a 6b and 6c*

The latter changes are very similar to those which Auerbach and co-workers reported in bronchi of humans who are heavy cigarette smokers. This similarity certainly justified a cautious optimism as to the validity of our experimental approach because it appears that exposure of animals to cigarette smoke is a useful approach, in spite of the realization that it is different from the actual process of cigarette smoking

The fate of this dysplasia in the bronchial epithelium of mice seemed, of course of particular interest even regardless of its possible causation by exposure to cigarette smoke The obvious questions which had to be answered are Is this dysplasia a precancerous state in other words, will it progress to invasive Carcinoma, especially when the exposure to cigarette smoke is continued during the whole life span? Will the alterations remain stationary or will they revert back to normal, especially when exposure is stopped? Although an extensive study which we have started along these lines is still under way we can already state that in none of the mice which have been exposed to smoke from up to 1,500 cigarettes over a period of nearly two years has an invasive bronchogenic Carcinoma been found. On the other hand, mice which had been exposed to cigarette smoke for three months or more and where exposure to smoke has



F gu 5 I t rruption f bas m t m mbran

that of tobacco smok Do you think that this benzpyrene comes from the combustion process or from tmospheric pollution on th spinach

I hav some more questions, too.—The first one is related to the real carcinogen in tobacco smoke There are two possibilities here One is that the real carcinogen is produced in the combustion process and especially by incomplet combustion. Another possibility which I consider equally interesting and worth investigation, is that combustion means detoxication of carcinogenic material and that incomplete combustion is also an incomplet detoxication. Your interesting results with different catalysts in cigarettes, particularly the results with calcium carbonat mak it h ghly probable that detoxication mechanism may play an essential role. I th presence of calcium carbonat more material—carcinogenic material—would be detoxicated. May I ask for you personal opinion in this field

Finally the co-carcinogenic effect. I can imagine that scientist working mostly with the skin of mice is ery much impressed by this initiating and promoting mechanism. But when working w th the subcutaneous tissue of rats one has the contrary iew viz. that it does not mean ery much. Because until now we do not know of any co-carcinogenic or similar initiating and promoting situation with regard to the subcutaneous tissue of the rat This is something specific for the skin of mic And I have some objections against considering the phenolic fraction as real co-carcinogen The co-carcinogenic action must, of course depend upon the dose in the same way as the carcinogenic action does. But the concentration of phenols or cresols in cigarett smoke condensate is, as Dr Carruthers showed, very small and I cannot imagine that this ery low concentration of phenols should hav such striking co-carcinogenic effect. So may I ask you, did you use your phenols in the same concentration as present in cigarette smoke condensate or in higher concentration

D W y d I was some very interesting questions that Prof Druckrey posed.—With respect to Japa one f the nteresting experiences in my own lif is tha in the field of epidemiology the world is our laboratory W hav been in Japan and I am doing lung cancer study in Japan together with Japanese colleague who is currently on my staff in New York. We were impressed, like you are, with the fact that lung cancer is less common in Japan than in the United States. First of all, dating back to 1930 the sales f cigarettes in Japan were one-third of that in the U.S. And I noticed difference in Japanese smokers which very much impressed me That is to say that particularly the elderly J panese smoker puffed his cigarette the way w smoke ou cigar I other words, I was impressed with the fact that the elderly Japa nese smoker did not inhale. My J panese friend and I ha just made study which confirms this that the cigarette smoker in J pa inhales considerably less than the American smoker Therefore the combination of less cigarette consumption with far less inhalation may be an important factor The younger Japanese smoker however begins to inhale the w y w do

I poi t to your question on statistics.—Of course as I said t the beginning of my talk, many of us look t the term statistics with suspicion. But I take it that if statistical study is done well, if it is done on much umber of cases and if it is properly evaluated, it gives us ery good information. A statistical study done in our section involves spending t least one hour with each patient, that is requiring all types of information which you then tabulate and cross-tabulate with the help of IBM systems. And we are forever conscious of looking for artificial variables that might explain finding which in itself ppears significant. The thing that impresses me about the relationship of smoking and lung cancer and which again came out in my discussions with Dr Mor ris in London few day ago, is that in man this relationship stands almost singularly there in th field of chronic diseases because of the magnitude of the relationship. I the terms of statistics, too, Dr Friberg yesterday presented some good studies on twins which will dd further to this field. I hope he will continue this in the greatest detail.

In respect to your point on inhalation it is indeed true that the question of inhalation is ery difficult to investigate. Because we hav also found that many smoker particularly today when he has some guilt-feeling may say to you, "Well, I don t inhale ery much when, in fact, upon observation you know that he inhales deeply

I respect to your question on filters it is indeed true that both chemically and biologically the presently available filter cigarettes are quite the same in the smoke condensate as the non-filter cigarettes. In other words, they do

then been stopped for more than three months, have frequently shown nearly normal bronchial epithelium, strongly suggesting reversibility of the changes, at least in some of the cases observed so far The decrease in the incidence of bronchitis and epithelial alterations after cessation is demonstrated in an example given in *Table I*

Of course we are aware of the pitfalls encountered when interpreting data indicating varying responses. Nevertheless, a decrease in incidence of the lesions is also suggested by our microscopical studies, in which we attempted to assess the sequence of this reversibility and where we have found that there seems to be a gradual desquamation of this atypical epithelium, followed by restoration of the normal one

B. *Cytochemical Changes.*

Turning now to the cytochemical studies, the characteristic results concerning the behavior of the DNA-proteins are shown in *Figure 7* These data are based on microspectrophotometric analysis of approximately 20 000 individual nuclei from 200 mice On the left, the DNA data are grouped, while the protein data are on the right. The correlated cytochemical studies of DNA and proteins in individual cells of bronchial epithelium of mice similarly did not reveal significant differences between mice exposed for two months and those exposed to cigarette smoke for a year or longer Regardless of dose or time of exposure, three types of cytochemical changes are found some mice which showed no significant histopathological le

TABLE I

FREQUENCY OF HISTOPATHOLOGICAL FINDINGS IN LEFT MAJOR BRONCHI OF MICE AFTER EXPOSURE TO CIGARETTE SMOKE WITH AND WITHOUT CESSATION PERIODS

Length of exposure to smoke in month	Number of cigarettes	Cessation period in days	Number of mice	Number of mice in relation to bronchial findings		
				No Significant Changes	Mild Bronchitis without or with Mild Epithelial Proliferation	Severe Bronchitis and Peribronchitis with Atypical Epithelial Proliferation
3—6	100—400	90 to 300		41	6	4
3—6	100 —400	NONE Sacrificed after exposure		39	7	17

everybody would do so. The third possibility is that C causes both A and B. This is the genetic hypothesis, so to speak, which implies that there is genetic constitution which makes people more liable to smoke cigarettes. And by virtue of the same genetic constitution they would also be more liable to develop lung cancer. W know little about the genetic determination of tumour susceptibility in mic and w even know little about it in man. W know that if we compare genetic determination mechanisms of different tumour types, such as adenoma of the lung or leukemia or mammary cance or adrenal tumours or tumours of the stomach, then all these are determined by multiple genes and each tumour has its ow genetic pattern of susceptibility. The pattern that determines the susceptibility to one tumour is not identical with the pattern that determines the susceptibility to another tumour. Each pattern is entirely different, and f we ha one tumou in which it is possible to analyze the rious components of carcinogenesis, then even here we can distin guish still further patterns which are still further different. For instance in breast cancer of the mouse there are certain genes that determine th susceptibility of the breast tissue to change into cancer there are other genes that determine the possibility of the milk gent to multiply in the mouse and there re still other genes that determine the right hormonal environment that is necessary for cancer production. All three of these patterns are determined by multiple genes, and all of them are different and do not coincide — If we then turn t smoking, which is what geneticist would call complex physiological characteristic, then there may be a genetic component, and Sir Ronald Fisher studies on twins indicate that this is indeed the case. But this is about the same type f physiological phenomenon as the ability of race horse to win rac which is physiological phenomenon with genetic component. There are multiple genes at action and the capacity of each gen to influence th final physiological characteristic is extremely remote— the ffect is ery remot on the haracteristic. T postulate then that this genetic component, which would influence smoking in humans, would be the same as that which would influence the susceptibility to lung cancer is, I think, about as probable as to suggest that two unrelated people would ha the same finger prints. I cannot see what other possibilities than that A causes B I smoking causes lung cancer could be really postulated biologically to explain the relationship which nobody seems to doubt exists, and I would be glad if anybody who wants to criticize the statistical evidence would forward another biological hypothesis.

free from virus. The second line is concerned with the effect of exposure to virus in addition to the exposure to cigarette smoke. If our concept is correct that viruses may act as co-factors in the production of the bronchial lesions, then mice which carry latent viruses prior to the exposure to smoke or which are infected with viruses should show frequent and perhaps more severe lesions, while mice free of virus should either be refractory or show mild lesions.

Although this is about all that we have to say here on the biological effect of cigarette smoke on the bronchi of mice, we should like to present a set of data concerned with the effect of cigarette smoke on the incidence of *spontaneously* occurring little nodules in lungs of mice, so-called adenomatous tumours, which are

TABLE IV

Frequency of Grossly Visible Adenomatous Lung Tumours in 166 Female CF Control (C) Mice and in 231 Female CF_1 Mice Exposed to Cigarette Smoke (E)

1 Age of Mice at Death Months	2 Groups	3 Time of Exposure to Cigarette Smoke Days	4 Number of Mice Examined	5 Mice with Adenomatous Lung Tumours Number	6 Mean Number %
3–7	C	–	45	1	2
	E	19–69	63	2	3
8–10	C	–	30	3	10
	E	17–99	16	5	37
	E	100–199	27	11	
11–14	C	–	33	14	42
	E	17–99	18	7	
	E	100–199	19	4	31
	E	200–600	4	2	
15–18	C	–	36	19	53
	E	17–99	13	5	
	E	100–199	8	4	57
	E	200–600	24	17	
19–28	C		22	13	59
	E	17–99	8	4	
	E	100–199	8	5	61
	E	200–600	23	15	
2–28	C		166	50	30 ± 7.0
	E	17–600	231	81	35 ± 7.0

question, it was felt that some fruitful information might also be obtained from studies on smaller *a imals exposed to ci garette smoke* if provision was made that the animals would inhale the smoke

In view of the fact that the majority of human lung cancers (nearly 90 per cent) take their origin in one of the major bronchi of the tracheobronchial tree, with only secondary invasion to the lung and since the columnar epithelial cells which line the lumina of the bronchi are more directly exposed to inhaled cigarette smoke than are the farther distant epithelial cells of bronchioles and alveoli in the lung itself studies of the tracheobronchial tree and particularly of the major bronchi, from animals exposed to cigarette smoke seemed especially pertinent. Surprisingly enough, to the best of our knowledge no systematic studies on the tracheobronchial tree from cigarette smoke-exposed animals had been published prior to our own studies, which we started several years ago.

Our work, which will be discussed here is a common effort in which, besides Dr Rudolf Leuchtenberger as pathologist, several young associates, namely Drs. Doolin and Zebrun and Miss Shaffer participated in various phases of the work.

II METHODS AND ANIMAL EXPERIMENTS

In order to cover several aspects of this complex problem, we attempted to study the sequential changes in the major bronchi of mice not only from a morphological but also from a chemical point of view Since the cell occupies a fundamental position in the living organism and is probably one of the primary targets hit by injurious agents, the sequence of events occurring in cells was assessed from a morphological and from a chemical point of view with special emphasis on the behavior of the DNA proteins. The significance of these intracellular substances for normal cell life, growth and genetic continuity is now fully recognized and hardly needs to be stressed any more. A quantitative study of the DNA-proteins seemed pertinent, since tumour cells are considered to be associated with abnormal DNA metabolism.

A. *Cytochemical Methods.*

For the exploration of the DNA-proteins we used the special quantitative cytochemical techniques of microspectrophotometry and interference microscopy Although we cannot discuss any methodical details, we should like to say a few words about these methods, especially about microspectrophotometry because these techniques are relatively recent and have opened completely new pathways for the study of the nucleoproteins. The development of these methods is based largely on work by Caspersson, who demonstrated that, by extending the optical properties of the microscope into the analytical sphere, the microscope can be used not only as the conventional tool for the morphological study of tissues and cells, but simultaneously as an instrument for the chemical analysis of the cell structure The basic principle of microspectrophotometry is actually very simple and closely resembles that so frequently applied in analytical chemistry As in the photometric chemical analysis of solutions, the amount of light absorbed by a cell structure at specific wavelength is used as a basis for the qualitative and quantitative analysis of the intracellular substances. Therefore a microspectrophotometer is actually nothing else than a microscope combined with a photometric device which permits light absorption measurements in single cells.

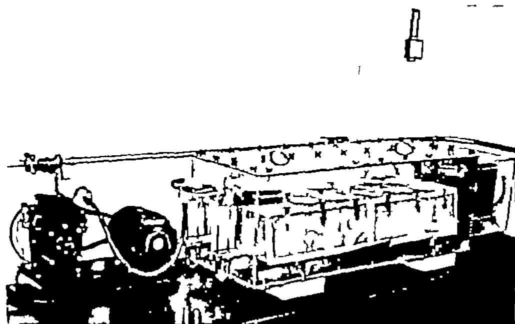
DISCUSSION

Prof Druckrey M y I ask you few questions, Dr Leuchtenberger I your experiments you used the principle of indirect smoking I this method the mice are exposed to an tmosphere containing increasing concentrations of carbon dioxide and carbon monoxide Doesn t this do any harm to the mice? Secondly indirect smoking in such cages will certainly lead t the formation of ggregates of smoke particles. And since we know that th action of erosols depend t high degree on the diameter of the particles, it may produce different effects

Then concerning your bronchitis effects, these re certainly you showed, unspecific and not related t lung cancer in specific way I think one can say so. And this seems to me to follow from your observations about the dose-response relationship. But, as far as I understood, the ariable factor was the time of exposure rather than the concentration of smoke in the air From pharmacological point of iew we hav to distinguish between different types of action. One is the function of the concentration never mind how long the exposure time is. The effects are reversible and your bronch tis effects seem to be related to this. Since the concentration was pproximat ly the same and only the time of exposure was changed, there is no wonder that th yield of effect was the same But on the other hand the carcinogenic effect which is irreversible does not depend pon concentration. The concentration does only determin the speed of dev lopment of the pathological hanges Th effect itself l the tumou yield, depends on th sum of ll exposures, the total dose as I tried to show So I think that t is quite understandable that you got the same bronchitis t different dosages, beca se you *used differences in time of exposure and not in* concentration and thus got concentration f fect and not summation effect

At European meeting concerning th problems of tmospheric poll tion and it long term toxicity hazards I had the pleasure of meeting my friend Prof Kotin from Los Angeles H told me tha he had succeeded in finding special animal which reacts with lung cancer H tested this for tmospheric pollution and was able to get lu g cancer in these pecial animals I hav forgotten wha special type of animals it w s. But ma I mention that t this European meeting which took place fortnight go there was of ourse lot of disagreement as to whether cigarette smoke or atmospheric pollution is the major cause of the increase in lung cancer I myself being in the unfortunate situation of being chairman t the meeting finally proposed to agree on the fact that the increase in lung cancer is certainly due to both factors—cigarett smoking and tmospheric pollution. And, as f r as I can see none f us is in a position at the moment to make quantitative decision—at least not on critical scientific basis—as to what is really the major or the minor cause Both re certainly causes, and we should try to do our best to reduce these ex posures as much as possible. And I am glad to say that there was complete and unanimous agreement on this from all the participants in our European meeting

D Leu htenberger Dr Druckrey concerning your f rst question as to th mortality of the mice in the smoking hamber I can only say that we noticed that when we put the mice I the first week in the smoking chamber we could only expose them to one cigarette daily Otherwise we had lethality But after this time we could increase the dose This may be due to the fact that we regulat our air flow t the pump accordingly so that the lethality to these poisonous gases seems to be zero under our conditions.—Concerning th particle ggregates I the smoking hamber it is indeed true that w very often see after long time exposure that there are some brownish aggregates but we have not looked into that.—Now concerning the dose effect relationship you poi ted out so correctly that we have increased the time but we thought that by also increasing the umber of cigarettes we *should ha an increase You see some mice* got only one or two cigarettes pe day for two months, and we would find th same lesions, what we call the most severe dysplastic lesion in bronchitis as in mic which had received up to six cigarettes daily for nearly their whole lifespan W could not always expose them so heavily because they sometimes lost weight and ppeared sick and we did not want mouse to die.—Now the argume t that perhaps our mic would never develop bronchogenic c r inoma of course has come to s, too But recently Dr Shields-Warren has used the same mic and h has used radioactiv cobalt and ha produced bronchogenic rcinoma Never



F gu 1

from the smoking chamber and placed in their cages, with food and water where they stayed until the next smoking period. Regular weighing of the mice showed that mice exposed to cigarette smoke frequently either lost weight or did not gain any as compared to the nonexposed control mice

At certain periods after exposure to cigarette smoke experimental mice and their controls were sacrificed. Blocks taken from the tracheobronchial tree and lung tissues, as seen in *Figu e* were immediately fixed and processed under the same tandardized conditions.

III *RESULTS*

A. *Histological and Cytological Chang*

Turning now to the experimental observations, t should be pointed out that one of the most striking results of our study is the ariability in response of the major bronchi from mice after exposure to cigarette smoke. The implication of this differ



Figure 2

ment in the lungs and if these animals had not had brown fur we would have believed that they were controls. The changes to which I referred and which Auerbach and Stout found, are nearly identical with those which occurred in the epithelium of the bronchi of our mice. As a matter of fact Auerbach at this time was very intrigued with these changes and said I should not stress so much the inflammatory changes. But since in our experiments we have never seen any epithelial proliferation without the bronchitis while we have seen a bronchitis without epithelial changes, we feel that actually the first step is probably the production of bronchitis and then, later on the epithelial change to hyperplasia and to dysplasia takes place. I think the development of bronchitis in mice is interesting because if we make here one comparison with human cigarette smokers, we all know that many of the heavy cigarette smokers have also brochitis.

Prof. Rengerts: I think that it is astonishing that among so many mice of a homozygotic strain treated in the same way so many were without inflammatory changes, while some had severe inflammatory changes.

Dr. Leuchtenberger: May I say that the mice which we used, CF_1 mice are not homozygotes. It is a hybrid strain. If we took 100 mice and exposed them under the same standardized conditions for the same length of time we always had this very large incidence of what we call no significant changes.



Figure 4. Papillary formation



Fig. 4b. Larger magnification of papillary formation.

(2) T Westermark, H. Lindroth An approach to the study of the chemical reactions of thermal gaseous ions with liquids and some notes on their possible biological effects, Arkiv för Kemi Vol. 17 No. 32
(3) T Westermark, L. Westfelt, H. Lindroth, N Ghanem Note on the Development of Methods for Studying the Polymerisation of Styrene and Acrylonitrile by Positive Gaseous Ions, Acta Chem. Scand *14* (1960) 1863–1864

A Method for Studying the Effect of Tobacco Smoke on the Ciliary Activity in the Trachea

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and
The Institute of Hygiene
Karolinska Institutet, Stockholm

The transport of mucus in the respiratory tract is a most important defense mechanism against inhaled particles and bacteria. A decreasing or completely interrupted transport of mucus opens opportunities for e.g bacteria to penetrate the mucosa with a following infection. Such an effect can either depend on changes in the secretion (such as amount and viscosity) or a change in the ciliary beat frequency With decreasing frequency of the ciliary beat there will be a slowing of the rate of mucus transport. It is therefore of great interest to investigate the effect of different substances on the transportation and ciliary beat. As known before pulmonary irritant gases t low concentration (about 10 ppm) very soon cause a stop in the ciliary activity in the trachea of living rats. Exposure to tobacco smoke causes the same reaction with the result that in few minutes after the beginning of the exposure the ciliary activity in most rats ceases. In these experiments, however the tobacco smoke was blown over the open trachea and the resorption effect of the nose was not taken into consideration. Experiments are under way however where rabbits are smoking tobacco through the normal respiratory path-ways.

A Twin Register for Studies of the Mortality in Smokers and Non-Smokers

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Karolinska Institutet, Stockholm

At the Institute of Hygiene Karolinska Institutet, and the Department of General Hygiene, the National Institute of Public Health investigations concerning mortality among smokers and non-smokers ill be carried out on a series of twins comprising all living Swedish twins of the same sex in unseparated pairs between 35 and 74 years of age in total about 38 000 twins about 14 000 of which are monozygotic.

In Sweden a representative register of twins can be compiled since complete birth records ha e been kept from the middle of the last century and these are readily available Moreover each death has been registered and the addresses of those still living can be traced through the local parish and county registers.

To date nominative punch cards for three-quarters of the twins born ha e been drawn up and the present addresses of those still living have been largely esta blished in ? out of 24 provinces. When all



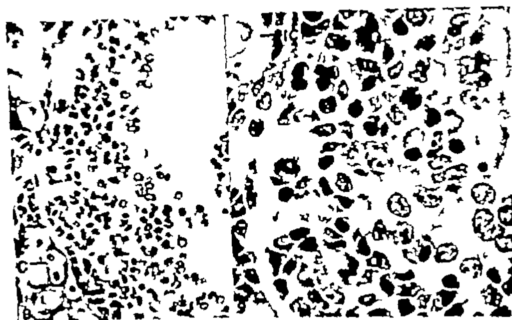
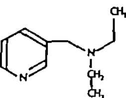
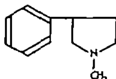


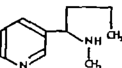
Figure 6a, 6b 6c Dysplasia in different magnifications.



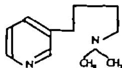
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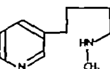
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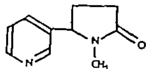
W 3



W 6



W 7



W 8

The activity on the rabbit's intestine was again highest for W 6 (0.15) and much less in other preparations. As regards the guinea pig ileum the strongest action was found in W 3 (0.04) W 6 (0.11) and W 7 (0.07) but lower in W 1 and W 2. Cotinine (W 8) was without nicotine action.

From the results it can be inferred that 1) the pyridine nucleus is not essential for the nicotine-like action, 2) compounds with an open pyrrolidine group may still have some 10 per cent of the action of nicotine on certain test objects.

On the Action of Nicotine on the Central Nervous System

C. R. Skoglund
Karolinska Institutet, Stockholm

By way of introduction it was pointed out that the pleasant stimulating effects of smoking on psychic functions are ultimately to be ascribed to a direct or indirect action of nicotine on nervous centers and, in addition that the mechanisms of this action, like those of any drug action on the central nervous system, may be rather complex, involving secondary effects due to changes in circulation or liberation of hormones. Some different research lines applied in the analysis of the various mechanisms of the central action of nicotine were exemplified.

In one series of experiments the action on different synaptic systems in the spinal cord of decerebrated or spinal cats was tested by injecting solutions of nicotine tartrate of different concentrations into the blood stream. Remarkably constant effects were found on the monosynaptic system, where inhibitory effects were observed at threshold doses of 50 micrograms of nicotine per kilo bodyweight corresponding to the blood concentration obtained in man by smoking one or two cigarettes. The effects on multisynaptic systems were more varying, both facilitation and inhibition being observed.

Another type of experiments served to illuminate the possible role of circulatory changes by measuring systemic blood pressure as well as blood flow in the spinal cord by inserted thermocouples. The results obtained so far indicated that the systemic pressure changes produced by nicotine injections at smaller doses were rather transient in the types of animal

sons contained a normal protein and DNA content, indistinguishable from that of nonexposed controls (upper histogram) some mice in spite of the absence of histopathological changes, revealed an increase in proteins (second histogram on right) but maintained a normal DNA content (second histogram on left) and, in the third type of change which w always present whenever epithelial proliferation was observed (third histogram) both DNA and protein content were increased in the nuclei of the bronchial epithelium. Cessation of exposure to cigarette smok (bottom histogram) was accompanied by DNA and protein values similar to those of the nonexposed controls. Sometimes, after cessation of exposure, DNA and protein values were even slightly lower than those n nuclei from unexposed controls

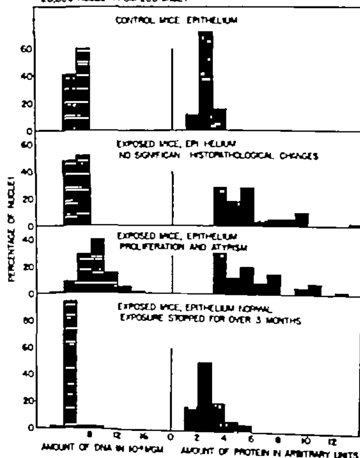


Figure 7

Table I Effect of smoking on plasma cortisol level in nonsmokers mcg = microgram.

Subject	Plasma cortisol, mcg/100 ml					
	Control day at			Experimental day at		
	9 AM	11 AM	1 PM	9 AM	11 AM	1 PM
M. N	15	8	4	14	12	6
A. R.	12	8	5	10	16	8
S H	9	7	5	11	18	11
P H	*9*	8	7	*9*	*14*	*10*
J S	13	6	4	12	17	9
K. S.	11	5	5	10	16	6
	No smoking			Two cigarettes between 9 10 AM		

Table II Effect of smoking on urinary Porter-Silber chromogens and aldosterone in nonsmokers. All values refer to urine collected between 9 AM–5 PM.

Subject	No smoking			Two cigarettes between 9—10 AM		
	Volume ml	17-OHCS mg	Aldosterone mcg	Volume ml	17-OHCS mg	Aldosterone mcg
M N	420	2.8	7	310	3.9	2
B. A.	440	1.7	4	170	2.6	2
S. H	540	3.7	5	430	4.2	1
P H.	610	3.4	8	470	4.5	3
H S	480	3.5	6	365	4.0	4
K. S.	510	3.2	3	480	4.6	2
A. R.	460	2.9	2	450	4.4	3

References

1 Eik Nes, K J Clin Endocrinol. & Metab. *17* 502 1957

2 Neher R. & Wettstein, A. J Clin Investig *35* 800 1956

3 Silber R H. & Porter C. J Biol. Chem. *210* 923 1954

quite different from bronchogenic Carcinoma. Several years ago, Essenberg using relatively small groups of mice reported that there was a striking increase in these adenomatous tumours in mice after exposure to cigarette smoke. However as can be seen from *Table II* under our experimental conditions controls and exposed mice reveal a very similar frequency which increases in both groups with age. They differ at only one point, which perhaps suggests a slightly earlier occurence in the exposed mice but actually the number of mice at this point is too small to draw a definite conclusion.

In I sing w hould I'ke to say that we r alize that our studie cover only a mall aspect of the many facet nvolv d n the problem of the biological effect of cigarette sm ke. Nevertheless the resemblance of bronchial lesions of mice exposed to cigarette smoke to those observed in human cigarette smokers justifies a cautious optimism *as to the valid ty of x perimental app oach in probing furth nto the c mpl x problem of the elation hip betw en cigarette smoking environmental facto s h st factors and dev lopment of lung can er*

theless you may be qu te correct that perhaps ou mice may not be the most sensitive model. There is, for instance one thing which somebody brought up when w discussed this problem. This was that these mice develop spontaneously othe adenomatous tumours, and it is possible that perhaps mice which have high incidence of adenomatous tumours may be less sensitive to develop bronchogenic carcinoma. W do not know And therefore w want to use now inbred train where the incidence of these is very low—I think these are ll the questions.

D W y der As Dr Druckrey mentioned, the particle size is, of course very important as to hether or not you are able to get the materials into the lungs I wonder whether you would care to comment on the failure of Dr Kuschner and his staff to produc bronchogenic arci noma in mice that were exposed to benzpyrene mist W clearly know that benzpyrene is carcinogenic to the bronchial tissue when you put thread with benzpy ene through the bronchus. But they were unable I belie to produce bronchogenic carcinoma by exposing mice to benzpyrene mist I ould like your iew as to whether one eason why you hav been unable so far to produc cancer is reall the fact that you do not get enough of this material into the bronchial tree

Secondly I wonder whether you think is possible to devis an experimen where you could directly introduce cigarette smoke condensate into the bronchial tree by perhaps ha ing a little intubation directly into the mouth, which would then lead into the lung and thus expose the animals After all, we know tha when man and mice were created, we were cr ted with ather efficient system of filtration and I would like to see an experiment done where w directl expose the animals the bronchial tree direc ly with tobacco smoke con densate I would like to kno w whether you are considering this or whether you think t is feasible

D Leu h enberg These are ery important questions Dr Wynder And particularly the question whether we really get enough of this tobacco smoke into the lungs Now Dr Mellors you ust ture was very much interested in this question, so he designed smoking machine And he showed that the exposure of mic and is under the conditions we had used there wer indeed very large parts in the lungs and in the cells. I have not discussed this because I was not oncerned with lungs today but we ha really found evidenc of phagocytosis of pigment after exposure to cigarette smoke So I do think that t gets into the lung

Concerning the experiments of Dr Kuschner —That he did not find ny bronchogenic car cinomas with benzpyrene I think is a ery important point. It raises namely this point is the tracheo-bronchial tree as sensiti to a car cinogen as is painting of the skin I mean, it eally boils down to what I think I tried to point out at the beginning namely that if we really want to test experimentally the relationship between cigarette smoking and bronchogenic carcinoma we should use an nimal which is losely related to the man, and w should let our animals smoke I think this is the most sound experimental approach.

The other question which you asked—I think it ould ertainly be done because Della Porta and Shubik ha done some ery beauti f l experiments I really don t belie that one can argue any more that mic just don t dev lop bronchogenic cancer since Dr Shields-Warren has shown that it can be done.

D Dalham Dr Druckrey has taken p the problem whether cigarette smoke or air pollution is the main cause of lung cancer and we ha just heard about Dr Leuchtenberger ex cellent studies on what happens morphologically in the respiratory tract when animals are exposed to cigarette smoke I hav some few slides which I would like to show They do not deal w th tobacco smoke. W hav taken p the problem of air pollution and ar trying to see what happens when animals are exposed to sulphur dioxide which, as you know is present in large amounts in polluted ai The animals used were rats, and we hav exposed them to 10 ppm for about month (Dr Dalham showed 6 slides) You see tha these findings are ery lose to what Dr Leuchtenberger has found e en working with tobacco smoke What is the main reason for the increase in lung cancer tobacco smoke or air pollution?

P of Ringertz (Prof Ringertz spoke away from the microphone and it has been impossible to reproduce his contribution from the tape recording)

D Leu htenberger Dr Ringertz, surprisingly enough over 50 per cent of all the mice which we exposed did not ha any inflammatory changes in the bronchi. They were really un distinguishable from those of the non-exposed controls and if we had not seen the brown pig

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Gaseous Ions and Their Possible Role in the Etiology of Lung Cancer and Some Observations on Free Charges in Cigarette Smoke

T Westermark,
Royal Institute of Technology Stockholm

Theoretical arguments are put forward to justify the idea that thermal positive gaseous ions of radical character possess a potential energy in the range 8–20 eV or much more than all known chemical bond energies (and also more than neutral free radicals) These ions thus should act radiation-like when brought into contact with liquid or solid matter Experimental results with positive helium and argon ions acting on typical radiation chemical liquid dosimeter systems such as dilute water solutions of $CHCl_3$ KI and Fe^{2+} and some gels support the assumptions The results indicate that the ions react in the surface layer of the liquid

A theoretical formula for the equivalent radiological dose is put forward as well as a Faraday law *Quantitat* ion dose calculations are thus made possible provided the electron affinity of the ion deposited and the mass of the substrate is known

The possibility of actions of gaseous ions in the human respiratory system is considered with this background. Since it is known that lung cancer can be induced by ionizing radiation it is logical to put forward the hypothesis that gaseous ions contribute to its etiology A physical condition to be fulfilled is that the potential energy of the ions should not be lost by aggregations sorption to dust or droplets etc matter which should be extensively studied in the future. Evidence is put forward that molecular ions from flames and electrical discharges are breathed by human beings. It was experimentally shown that free charges are present in motor car gases, often in ample quantities (1) (It is suggested that neutral free radical are also present in large quantities) Free charges of yet unknown kind has been detected in cigarette smoke. The order found is 10^{9} per cigarette They are probably not of very light kind. Thus man often breaths air containing elevated ion concentrations. This is the case in traffic (cars etc) in industry (various flames, electrical discharges, welding) in homes (cooking flames, bread toasters, radiation heaters) and further smokers inhale ions (see above)

Attempts to calculate the equivalent ion dose to the epithelium of the mucous membrane is met with several difficulties. Certain reasonable assumptions were made and showed that an ion concentration of $15000/cm^3$ would correspond to the radiological tolerance occupational limit of 100 mr week, provided these ions deposit all their energy to the human tissue By making the yet hypothetical assumption that the charges found from cigarettes are radiomimetic a 20 cig/day smoker will get some 20 rad/year which gives a lung cancer incidence of 0.5 per cent per year

A more detailed paper has been published (2) as well as a special study (3)

Note added Febr 1961 K. H. Kingdon has recently (Nature *189* 180 [1961]) put forward a similar lung cancer hypothesis as the above one. The arguments given are qualitative but nevertheless very interesting –It seems that the whole problem complex should now be attacked experimentally in every detailed step

(1) T Westermark Detection of free charges from motor-car exhaust gases, Nature *189* (1961) 910

) The underlying studies have been supported by grants from AB Svenska Tobaksmonopolet.

Translated by Dr Donald Pagden

These investigations have been supported by grants from Statens Medicinska Forskningsråd, Sweden and Swedish National Association against Heart and Chest Diseases.

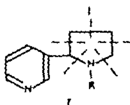
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the relevant addresses have been obtained the twins will be contacted to diagnose their genotype, smoking habits and certain variables of sociological background. The genotype diagnosis is clearly of fundamental importance. It can be established with almost complete certainty by blood group analysis. We intend however to use similarity diagnoses on the total material, based on questionnaires. There is reason to suppose that in this way at least the diagnosis of the monozygotic twins can be established with over 93 per cent certainty. This form of diagnosis will be evaluated by comparison with blood group diagnoses carried out at the same time on a random sample.

Synthetic Analogues of Nicotine

I. Wellings
Royal Institute of Technology, Stockholm

Some of the more interesting methods of synthesis used in the preparation of several series of nicotine analogues were described. One of the series was that formed by opening of the pyrrolidine ring of nicotine (I. R = CH_3) in the various possible ways.



Another series discussed was that in which the pyridine ring of nicotine had been replaced by a benzene ring and the open chain derivatives of this type.

Finally some derivatives of nornicotine (I. R = H) in which the hydrogen in the pyrrolidine ring had been replaced by alkyl groups of different size were described.

The physiological activities of these compounds in relation to the activity of nicotine were presented in a subsequent paper.

Biological Actions of Synthetic Analogues of Nicotine

U. S. von Euler
Karolinska Institutet, Stockholm

It is known that pyrrolidine like piperidine exerts typical nicotine like actions although the activity per unit weight of these compounds is only about 1/15 of that of nicotine itself. With a view to studying relationships between structure and pharmacological action some synthetic analogues of nicotine (prepared by Dr I. Wellings) have been assayed on the cat blood pressure and on the isolated jejunum of the rabbit and the guinea pig. The activity is expressed in relation to nicotine base (= 1).

The highest activity on the cat's blood pressure was found in compound W 6 (0.1) while the activity of the corresponding monomethyl compound (W7 dihydrometanicotine) was less (0.05). In other compounds with an open pyrrolidine group the activity was smaller but still present (W 3). In W 2 where the pyridine nucleus was substituted by a benzene ring the activity on the blood pressure was high (0.22)

PART TWO

PART THREE

preparations used while the local decrease of blood flow in the cord which considerably outlasted the systemic effects might possibly contribute to the long-lasting effects observed on nervous transmission.

A late phase of local vasoconstriction sometimes observed led to considerations of the possible influence on spinal cord of adrenaline or noradrenaline liberated by the nicotine injections. A comparative series of experiments on the effects of noradrenaline injections showed that spinal interneuron activity may undergo both facilitatory and inhibitory changes. Liberation of these substances has therefore to be taken into account as a secondary factor in central nicotine action.

It appeared that in order to elucidate the direct action of nicotin on nerve cells, a better knowledge of it effect on fundamental membrane processes was required, and some preliminary results from a series of experiments on muscle membrane with i tracellula technique started for this purpose were finally reported.

The Effect of Smoking on the Production of Adreno-Cortical Hormones

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The production of adreno-cortical hormones was followed by the determination of plasma cortisol le 1 (1) and urinary excretion of Porter-Silber chromogens (17 OHCS (3) nd aldosterone (2)

In nonsmokers the consecutive smoking of two-thirds of two nonfiltered cigarettes with inhalation wa ucceeded by a marked increased in plasma cortisol (Table 1) within 2 hours after a f rther 2 hours the values approached control levels Urinary 17-OHCS likewise rose although rather moderately a revealed by values obtained from urines collected for the next 8 hours following smoking (Table 2) Urinary aldosterone determined in the same samples, on the other hand, fell almost invariably and urinary olumes decreased concomitantly (Table 2)

In habitual smokers, having smoked 3 cigarettes in the morning plasma cortisol levels were 12.3 ± 0.9? mcg/100 ml at 10 AM when abstaining from their morning cigarettes the same subjects showed plasma cortisol of 12.4 ± 1.18 In non-smoking controls the level was 11.0 ± ± 1.24 Urinary 17-OHCS were 4.9 ± ± 1.32 mg/24 hrs in habitual smokers on their ordinary cigarett consumption, as compared to 4.5 ± 1.45 in nonsmoking controls. In 10 chronic smokers urinary aldosterone varied between 2—18 mcg per day with mean of 7.6, whereas nonsmokers varied between 1—10 with a mean of 5.4 When urinary aldosterone was repeated in smokers presenting higher than normal alues, figures well within the normal range were obtained

The present data indicate that acute smoking stimulates the pituitary adrenocortical system leading to increased cortisol production. It should be noted that the nonsmokers in connection with smoking experienced nausea and cardiovascular reactions. The simultaneous decrease in aldosterone production gives further support for its independence of ACTH and is noteworthy because of its unusually rapid occurrence.—In habitual smokers adaptation seems to have taken place as revealed by "normal" cortisol production. The significance of occasional high aldosterone values in smokers is not clear

used as a detector for ultrasound, since the latter causes mechanical vibrations in the crystal, which in turn generates electric charges on its surfaces.

The passage of sound through a homogeneous medium.

During the passage of sound through a medium, the particles of which that medium consists are thrown into vibration, either in the line of propagation of the sound or at right angles to it. Thus one speaks of longitudinal and transverse waves, respectively. In solid bodies both types of wave occur together with other more complicated waveforms — see Bergmann (15) but in gases and fluids only longitudinal waves are possible. In the latter case the wave movement consists only of alternate compressions and expansions in the medium along the line of propagation of the sound. According to Frucht (46) mainly longitudinal waves occur in animal tissues, there being only weak transverse waves. For practical purposes therefore, one can disregard these latter.

These waves are governed by the following equations [see Bergmann (15)]. The particles in the medium oscillate to and fro. The maximum velocity S reached during oscillation is given by the equation

$$S = \sqrt{-\ I\ 10}\ \text{cm sec} \qquad (1)$$

where I = sound intensity in watts/sq cm or the energy which is passing through 1 sq. cm of the beam's area per second, ρ = density of medium, v = velocity of sound. The amplitude of vibration A is derived from the equation

$$A = \frac{1}{\omega}\sqrt{\frac{2\,I\,10^7}{\rho\,v}}\ \text{cm} \qquad (2)$$

where $\omega = 2\pi f$ and f is the sound frequency.

The maximum acceleration a of the particles is derived from

$$a = \omega\sqrt{\frac{2\,I\,10^7}{\rho\,v}}\ \text{cm/sec.} \qquad (3)$$

As a result of this violent oscillation of the particles, maximal dilatating forces and maximal compressing forces, separated from each other by half a wave length, occur along the axis of the beam. This alternating pressure or sound pressure amplitude P is expressed by

$$P = 2\pi f \rho v A \ \text{dynes/sq. cm} \qquad (4)$$

P can also be expressed in atmospheres, 1 atm. = 931×10^3 dynes/sq. cm.

The velocity of sound in a medium depends on the density and compressibility of that medium. In the majority of fluids the speed of sound is between 1000 and 1600 metres per second. In water the figure is 1497 m/sec. according to Bergmann (15) and 1501 m/sec. according to Goldman et al. (58). Ludwig (109) and later also Goldman & Richards (58) studied sound velocity in various organs and tissues in animals. Goldman & Richards reported a figure of 1572 m/sec. using frequencies of 1, 2, 4 and 12 Mc/s for dogs' heart muscle.

Frucht (46) gives the following values for the velocity of sound in human tissues at freq. 1.8 Mc/s.

muscle refrig.	1568 m/sec.
liver refrig.	1570 m/sec.
fat	1476 m/sec.

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SUPPLEMENTUM 370

ULTRASOUNDCARDIOGRAPHY

INGE EDLER The use of ultrasound as a diagnostic aid, and its effects on biological tissues.
Continuous recording of the movements of various heart structures using an ultrasound echo-method.

INGE EDLER ARNE GUSTAFSON TORD KARLEFORS and BO CHRISTENSSON Mitral and aortic valve movements recorded by an ultra-sonic echo-method. An experimental study

INGE EDLER Atrioventricular valve motility in the living human heart recorded by ultrasound.

Accompanies vol. 170

dence and refraction, v_1 and v_2 are the velocities of sound in the respective media.

The absorption of sound.

During passage through a homogeneous medium, sound intensity becomes progressively diminished as a result of absorption and scattering. Absorption implies that the amplitude of sound waves is weakened primarily by "inner friction or viscosity"

In a given fluid or gas the residual intensity I, after a plane sound wave of initial intensity I_0 has travelled the distance x, is given by the equation

$$I = I_0 e^{-2\alpha x f^2} = I_0 e^{-2\alpha x} \qquad (7)$$

where f is the sound frequency and α is the amplitude absorption coefficient. The absorption factor thus varies as the square of frequency The distance required to reduce the intensity of a given signal by half is called the half value layer According to Pohlman (128) this is derived from

$$I = I_0 2^{-\frac{x}{H}} \qquad (8)$$

where H = half value layer

Hüter (80) and Pohlman (86) have carried out measurements of sound absorption in various tissues, and shown that it has a linear relationship to frequency

$$I = I_0 e^{-2\alpha f} \qquad (9)$$

In vitro experiments by Pohlman (123) gave 2.4, 1.1 0.8 and 0.4 cm as the half value layers in heart muscle for frequencies of 0.8, 1.5, 2.4, and 4.5 Mc/s, respectively According to the same author (122, 127) the result in the case of gluteal muscles is 3.6 cm in vitro, and 2.1 cm in vivo using a frequency of 0.8 Mc/s. For fat in the gluteal region the figures are 6.8 cm and 3.3 cm, respectively at the same frequency

Absorption coefficients and half value layers for different human tissues, as compiled by Goldman & Hüter 1956 (57) are given in table 2.

Table 2.

Tissue	Frequency Mc	Amplitude absorption coeff cm-1	Half value layer cm
Plasma	*1.0*	*0 007*	*100.0*
Blood	1.0	0 02	35.0
Fat	0.8	0 05	6.9
Muscle	0.8	0.1	3 6
Brain, fixed	0.87	0.14	2.5
Liver 20 hrs post mortem	1 0	0.15	2.4
Skull bone, fresh or fixed	0.8	1.5	0.23
Sciatic nerve sound travelling in direction of fiber axis	3.4	0.35	1 0
Sciatic nerve, sound travelling perpendicular to fiber axis	3.4	0.55	0.63

Hüter & Pohlman (86) have stated that for tongue muscle the degree of absorption is smaller when measured lengthways than when measured transversely (with respect to the longitudinal axis of the muscle fibres) This is likely to depend not on increased absorption, but on increased reflection of sound when travelling at right angles to the muscle fibres. Wild & Reid (145) have shown

FROM THE DEPARTMENT OF INTERNAL MEDICINE, UNIVERSITY HOSPITAL LUND SWEDEN
HEAD PROFESSOR H MALMROS

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angle of divergence, α, for the beam (i.e.half the angle formed by the apex of the cone) is derived from

$$\sin \alpha = \frac{0.61\lambda}{r} \qquad (11)$$

The smaller the wavelength in relation to the radius of the soundgenerating surface, the smaller will be the spread of the sound, and the more well defined and intense the beam.

From formulae (10) and (11) it is apparent that a well directed beam can only be obtained if the wavelength is considerably less than the diameter of the sound-generating crystal. If for example the ratio wavelength-diameter of crystal, is 1 10 then according to formula (10)

$$l = \frac{r^2}{\lambda} = \frac{r^2}{\frac{r}{5}} = 5\,r \qquad (12)$$

and according to formula (11)

$$\sin \alpha = \frac{0.61\lambda}{r} = \frac{0.61\,\frac{r}{5}}{r} = 0.122$$

$$\alpha = \qquad (13)$$

If instead, 1:20 is chosen as the relationship between wavelength and crystal diameter then l becomes 10 r and angle α = 3.5

Choice of frequency

As mentioned previously (page 12) the penetrating power of sound diminishes with increase in frequency whereas its resolving power increases and beam spreading is reduced. To obtain greater range therefore one must use low frequencies (less absorption) but if the object is to restrict spreading to obtain high resolution, then high frequencies must be used. The choice of frequency thus becomes a compromise between these conflicting interests.

Preliminary investigations by Hertz and the author (34 72) revealed that with the apparatus we use, echo signals can be obtained from the deeper parts of the thorax in adults using frequencies of 2.5 Mc/s. Only in the very obese and sometimes in patients with advanced emphysema was one obliged to reduce the frequency to 1 Mc/s in order to obtain comparable echo signals. (The apparatus in question is capable of working at frequencies of 5, 2.5, 1 and 0.5 Mc/s) In thin patients and especially in children 5 Mc/s proved satisfactory For these reasons it was therefore decided to work with a frequency of 2.5 Mc/s, and only in exceptional circumstances to resort to 1 or 5 Mc/s.

According to the investigations referred to on page 10 the velocity of sound in muscle and other tissues is in the region of 1500 metres per second. At frequencies of 1, 2.5 and 5 Mc/s the wavelength in these media are 1.5 0.6 and 0.3 millimetres respectively

Table 3

Frequency	Wavelength	Length of nearzone, l	Angle of divergence
1 Mc/s	1.5 mm	24 mm	8.8
2.5 Mc/s	0.6 mm	60 mm	3.5
5 Mc/s	0.3 mm	120 mm	1.75

Table 3 shows the length of the near zone and the angle of divergence at the various frequencies when the diameter

CONTENTS

frequency in cycles per second and ρv the acoustic impedance of the medium, in which the sound is propagated.

In the studies described quartz crystals were used initially for production of ultrasound. It became apparent, how ever that in order to obtain good recordings it was necessary that the maximum sound pulse intensity be as great as possible. A substantial improvement was obtained in this respect when quartz was replaced by barium titanate, which because of its piezoelectric characteristics is able to generate greater sound intensity and to act as a more sensitive receiver for echoes. By connecting the crystal to the transmitter via a small high frequency transformer which is built into the crystal holder the sensitivity can be further improved, so that the maximum impulse intensity in present day crystals is of the order of 40 watts/sq cm at 2.5 Mc/s. For further details see table 4.

INTRODUCTION

Since the end of World War II the developments within the sphere of heart surgery have created increasing demands for diagnostic precision. Prominent among those conditions which have now became amenable to treatment is mitral stenosis. In selecting such cases for commissurotomy it became apparent that current methods for investigating cardiovascular function, such as heart x rays, phonocardiography pressure measurements during cardiac catheterisation etc. often gave insufficient information. Thus it was deemed desirable to find a method of recording the movements of the heart walls or the volume fluctuations of the heart cavities during the cardiac cycle.

The cardiac borders as visualised on the fluoroscopic screen can be recorded by means of an electrochymograph, but this method gives no information as to the heart's internal surfaces. The form, size and volume fluctuations of the heart chambers can be studied by angiocardiography but this method is complicated, permits only a very limited period of study and cannot be repeated in the absence of urgent indications. With the object of visualising the individual movements of the various parts of the heart, (and thereby being able to distinguish, among other things, between stenosis and incompetence of the mitral valve) Hertz and the author in 1953 started to use the ultrasonic echo method (34) In industry this method had been well known for some years, as applied to the non-destructive testing of materials for the presence of flaws.

This paper gives an account of the method we have developed for cardiological investigations. Further the possibility of recording movements of the heart walls and valve cusps is demonstrated.

to the constantly altering relationships between blood and heart muscle on the one hand, and lung tissue on the other along the path traversed by the sound. Keidel used a frequency of 60 kc/s. This technique gave no quantitative information about cardiac volume changes. Apart from the original paper describing this method no further information has appeared.

A more practical method of using ultrasound for medical diagnostic purposes is the reflection technique, in which both transmitter and receiver are placed on the same side of the object under examination. Very short sound impulses are emitted at relatively long intervals. A fraction of the sound is reflected at each interface while the greater part passes on into the deeper tissues. Recordings are then made of the amount of sound reflected by the tissue interfaces. This possibility was described by Gohr & Wedekind (56) 1940, who, however did not publish any subsequent results.

The first report of the practical use of this method was in 1949 by Ludwig & Struthers (110) who attempted thereby to detect gallstones and foreign bodies buried in the muscles of dogs. These workers gave as their opinion that the multiple reflections which they obtained from the soft tissues were too erratic to be of practical value. They suggested, however that refinements in technique might make the detection of tumours possible.

In 1950, Wild (140) published a preliminary report of an investigation, using the reflection method to examine biological material. He obtained multiple reflections from cancer tissue in a preparation made from resected stomach.

French, Wild & Neal (43) at post mortem examination of a case of cerebral tumour obtained similar echoes from the tumour area in the removed brain. Experiments were then made on animal brains in vivo, using the same apparatus, and no harmful effects were observed (44) Following this work Wild, Neal & Reid (142, 143) began to investigate patients with breast tumours. In 1952 Wild & Reid published a series of 21 such cases. Their findings were that in general, cancerous tissue reflected more sound than normal control tissue and that the tissue of non malignant tumours reflected less than did control tissue.

In 1952 Wild & Reid (144) gave an account of their development of a two-dimensional method of visualising living tissues with their original apparatus. They recorded a two-dimensional echogram by moving the sound beam through the tissues in synchrony with the trace on the oscilloscope screen. They continued with this method and in 1956 Wild & Reid (146) reported the results of examination of 77 palpable abnormalities in the human breast. Of these, 27 were malignant, and all but one of them had a typical echogram. Of 50 benign tumours 43 had an echogram of non-malignant type, and seven of malignant type.

Howry & Bliss (77 78) using a similar two-dimensional method, recorded cross sectional pictures of the extremities in living subjects, as well as of benign and malignant breast tumours in vitro

Chapter I

SOME PHYSICAL PROPERTIES OF ULTRASOUND*)

All sound with a frequency above 20000 cycles per second (c/s) is usually regarded as ultrasound. Such high frequencies can not be detected by the human ear for which the upper limit is about 18000 c/s in children and young people gradually decreasing with age. With modern devices frequencies of up to 10^9 c/s [$= 10^6$ kilocycles per second (kc/s) $= 10^3$ megacycles per second (Mc/s)] can be produced.

The acoustic laws which govern the behaviour of low frequency sound (that detectable by the human ear) hold also for ultrasound. However the latter has certain special characteristics which do not generally appear at low frequencies. Thus ultrasound can be beamed in a given direction and also bent or refracted by special means.

Ultrasound can be generated by inducing a crystal to vibrate by means of an electric current. In 1880 the brothers Curie showed that electric charges appeared on the surface of a suitably cut plate of quartz if it was subjected to mechanical stresses. This so called piezoelectric effect can be evoked in a variety of crystal types such as quartz, lithium sulfate, Rochelle salt etc. Nowadays crystals of barium- or leadzirconium-titanate are often used for this purpose. The property common to all piezoelectric crystals is that they have one or more polar axis, i. e. that they lack a centre of symmetry

In 1881 the Curie brothers discovered the reciprocal piezoelectrical effect If a piezoelectric crystal is suitably placed in an alternating electric field it will be thrown into vibration in a characteristic fashion. It was not until 1917 however that Langevin succeeded in producing the first piezoelectric ultrasound generator By matching the frequency of the alternating field to the resonant frequency of the crystal, the resonance thereby invoked in the latter produced powerful mechanical vibrations which were then transmitted through the surrounding medium as ultrasound waves. Such a crystal plate, when connected to suitable apparatus can also be

*) For a detailed study of ultrasound see Bergmann, L. Der Ultraschall (15)

λ = wavelength of ultrasound in biological tissue. The frequency of the beat is proportional to the velocity component of the target. The Doppler signal was recorded by means of an electromagnetic oscillograph. Yoshida, Satomura et al. (149) have recently published an account of the clinical uses of the method and this will be discussed in part III.

Gurevic & Sobakin (60 a) in a recent review of the use of ultrasound in the diagnosis of disease in internal organs, *produced a two-dimensional representa* tion of the heart in vitro. The method seems as yet, however to have no prac tical value. Hertz et al. (35 a, 72 a) are also working with such a method.

Kalmus (91) has described an acoustic flowmeter which has as its principle the measurement of the difference in transit times for the transmission of sound upstream and downstream between two similar transducers spaced on the outside of the liquid-carrying tube. Herrick et al (69) and Franklin *et al.* (42) have used this method for measuring blood flow Franklin, using dogs, has measured the transit time taken for pulsed ultrasound to pass diagonally across the root of the aorta. The sound travelled more quickly with the stream than against it, and the difference was proportional to the mean velocity of blood flow in the aorta.

Rushmer et al. (130) have used ultrasound for measurement of the diameter of the ventricular cavities in dogs. The transit time of ultrasonic waves between two crystals mounted on opposite sides of the chamber can be continuously recorded.

Leksell (105, 106) *introduced* echoencephalography (uni-dimensional method) in 1954, and showed that it was possible to demonstrate post traumatic intracranial haemorrhages in children. He also found that in the major ity of adults as well as in children a characteristic midline echo was obtain ed, the origin of which was attributed to the pineal body Gordon (59) who adopted Leksell's method, considers that the midline echo arises rather from the septum pellucidum than from the pineal body *Further studies of the origin* of this midline echo, together with experience with echoencephalography in a large series of cases is reported by Jeppsson (89 90) Jeppsson showed that in children the echo-giving struc tures are the septum pellucidum and the walls of the third ventricle, while in adults the pineal body is responsible because *of its high acoustic impedance.* Vlieger & Ridder (138) and Lithander (107 108) have also published work on echoencephalography

At The Second International Congress on Acoustics, June 17th to 23rd, 1956 at Cambridge, Massachusetts, U S. A. Kikuchi & co-workers (94) reported that they had used an ultrasound pulse *method for the early diagnosis of* mam mary cancer (obtaining multiple irregular echoes) On the other hand, benign tumours of the breast gave no characteristic echo *and they could not be* distinguished from the normal breast tissue. These authors also reported that they had studied echoes from human cerebral ventricles, brain tumours, abdominal tumours and gallstones. As men tioned previously they also made the

Ludwig (109) has reported that in limbs at body temperature the speed is *between 1490 and 1610 m/sec., averag* ing about 1540 m/sec. the correspond ing frequency being 2.5 Mc/s) In bone the speed is considerably higher Thus according to Theismann & Pfander (137) it is 3360 m/sec. in human skull bone at body temperature and 0.8 Mc/s. Further details can be found in Goldman & Hüter's article (57) in which the *results of researches* by a variety of authors are assembled

The passage of sound through an interface.

When an interface between two media having different densities, and through which sound passes at different speeds is struck by a sound wave the latter is partly reflected, and in part continues onwards through the second medium. The reflection of the sound is governed by the well known law angle of incidence equals angle of reflection.

The product of the density of a medium, ρ and the speed at which sound passes through it, v is called the acoustic impedance, ρv of that medium. If the sound wave strikes the interface at *right angles, the reflection index, R,* that is the proportional constant between the reflected and incident sound intensity is given by the equation

$$R = \left(\frac{\rho_1 v_1 - \rho_2 v_2}{\rho_1 v_1 + \rho_2 v_2}\right)^2 \qquad (5)$$

where ρ_1 and ρ_2 are the densities, and v_1 and v_2 the velocity of sound in the respective media. Thus the greater the difference in acoustic impedances between the two media, the greater becomes the reflection index.

The acoustic impedance ρv in different human tissues according to Güttner (62) is shown in table 1.

At a bone/muscle interface, roughly 30 % reflection of energy occurs, when the incident angle of sound is 90

When sound crosses an interface between two media it undergoes refraction. This process is governed by Snellius' law

$$\frac{\sin \alpha_1}{\sin \alpha} = \frac{}{v} \qquad (6)$$

where α_1 and α_2 are the angles of inci

Table 1

Tissue	$\rho v\, 10^{-5}$ gr/sq cm sec.	ρ in gr/cm
Fat	1.36	0.97
Muscle	1 63	1.04
Brain	1.56	1.03
Compact bone	6.1	1 07
Cancellous bone	2.2—2.9	—
Blood	—	1 0
W ter	1 49	1 0

Finally it should be mentioned that ultrasound has been used in another entirely different way in medical work. Keidel (93) described in 1950 a method for estimating the CO_2 content of expired air. CO_2 absorbs ultrasound to a significantly greater extent than the other constituents of expired air and the degree of absorption therefore constitutes a measure of the CO_2 content.

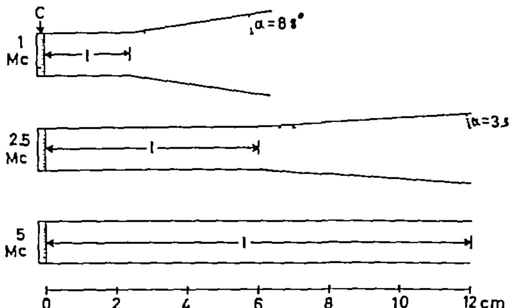


Fig 1. The "near zone" at frequencies of 1, 2.5 and 5 Mc/s in a medium in which the velocity of sound = 1500 m/s. The diameter of the sound generating crystal is 12 mm. l = the length of the near zone α = the angle of divergence. Cf. table 2, page 14.

that the echoes are significantly reduced, when the muscle fibres are parallel to the sound beam, compared with when they are at right angles to it. The echoes were considered to arise from the interfaces between the muscle bundles and intervening connective tissue.

Lack of homogeneity in a medium brings about a reduction in the intensity of transmitted sound because of reflection, scattering and refraction.

Behaviour of sound in the proximity of the sound source (ultrasonic generator)

In the immediate vicinity of a cylinder-shaped ultrasound generator sound energy is emitted as a cylindrical beam of like diameter (actually slightly constricted) (Fig 1) The sound within this zone is not homogeneous because of interference. The length, l, of this so called "near zone" is derived from the following formula, [Pohlman (124)]

$$l = \frac{r^2}{\lambda} = \frac{r^2 f}{v} \qquad (10)$$

where r is radius of sound generating surface, λ is the sound wavelength in the medium in question, f is frequency and v is velocity of sound in that medium.

It can be deduced from this formula that the length of the near zone varies as the square of the radius and the reciprocal of the wavelength (and thus directly with frequency)

Beyond the near zone the beam widens out into a cone implying a reduction in sound intensity as distance from the transducer increases, Fig 1 The

cified) of the thorax and aortic area. Immediately after treatment the patient felt ill, and after progressive deterioration died on the third day Autopsy revealed rupture of a grossly atheromatous aortic arch.

Other authors saw no complications in large series of patients. Thus Demmel (23) in 1951 reported the results of ultrasound treatment applied to different parts of the body in approximately 2000 cases. During follow-up examinations, which he generally carried out for several months after treatment, he saw no evidence of permanent damage. During continuous exposure patients sometimes experienced a sensation of warmth, and Demmel occasionally observed blistering of the skin, and in a few cases, petechial haemorrhages. Demmel has also irradiated the precordial region in two volunteers for 6 and 8 minutes respectively using a sound intensity of 30 watts from a crystal of 10 sq cm surface area i. e. an output of 3 watts/sq cm. The frequency used was 1 Mc/s. The subjects of this experiment experienced minimal discomfort. ECGs before and after treatment showed no pathological changes. A certain degree of tachycardia was observed however

Koeppen (95, 96) in 15 patients aged between 23 and 65 years, irradiated the precordium with ultrasound at an intensity of 1 to 4 watts/sq. cm and frequency of 0.8 and 0.175 Mc s without detecting any effect on the heart or circulation. Each patient received continuous irradiation for 10 minutes on from 3 to 6 different occasions. Repeated ECG examinations were carried out, and the patients remained under observation for 4 to 8 weeks after the conclusion of treatment. Pohlman (126) who has had much experience of ultrasound therapy advises that treatment can safely be commenced with 0.3 to 0.8 watt/sq. cm. If this proves inadequate the dosage can then be raised progressively to 2, 3 or 4 watts/sq cm. From 15 to 20 such treatments can be given, each lasting 5, 10 or 15 minutes, being carried out with massageing movements of the crystal and using liquid paraffin or glycerin to improve contact with the skin. Frequencies of from 0.175 Mc/s to 3 Mc/s have been used without injuries or other side effects being seen. Because, however of the aforementioned complications reported by Buchtala & Hertzog, Pohlman advises against irradiation of the precordium in patients with angina pectoris. He furthermore maintains that in those cases where serious complications have been met with, the "therapeutic dose" has been substantially exceeded (122) If a stationary crystal is used Pohlman recommends that the intensity should be accordingly reduced to 0.2—0 4 watt/sq. cm. The crystals have as a rule an emitting surface of 5 to 10 sq cm.

Buchtala (18) in using continuous ultrasound in therapy employed a fixed crystal giving 0.5—1.2 watts/10 sq cm i. e a maximum of 0.12 watt/sq cm. When it was desired to irradiate a localised area or a specific structure such as the stellate ganglion or the sciatic nerve, the output could be momentarily raised to 1 watt/sq cm with

of the sound source is 12 mm and the velocity of the sound 1500 metres per second.

At 2.5 Mc/s one thus has a beam which is cylindrical for a distance of 60 mm from the crystal. With 3.5 divergence the diameter of the beam is increased twofold at about 100 mm (98 mm to be exact) from the end of the near zone, and the cross sectional area has increased from 113 sq mm to 452 sq mm. At 100 mm from the crystal (60+40 mm) the cross sectional area is doubled.

At a frequency of 1 Mc/s the sectional area of the beam is increased twofold 16.1 mm from the end of the near zone, i.e. 40 mm (24+16.1 mm) from the crystal. 63 mm (24+38.8 mm) from the crystal it is increased four fold.

) In most of the examinations a crystal of 12 mm diameter has been used.

From these calculations it can be seen that 1 Mc/s can be used with advantage for structures not exceeding 40 mm distance from the crystal, and 2.5 Mc/s for those not exceeding 100 mm distance. Practical experience has shown, however that when carrying out examinations of the heart (and chest) in man, echo signals can be recorded from structures up to 150 mm distant from the crystal, both with frequencies of 2.5 and 1 Mc/s.

Sound intensity

The intensity of sound I generated by piezoelectric quartz crystals can be calculated from the resonance frequency of the crystal, and the voltage applied. The relationships are expressed by the formula

$$I = \frac{1.44 \times 10^{-18} U^2 f^2}{\rho v} \text{watt/sq cm} \quad (14)$$

U=applied AC potential in volts, f=

Table 4

Sound frequency	Mc/s	1	2.5	5
Wave length in soft biological tissue	mm	1.5	0.6	0.3
Maximum Intensity of ultrasound impulse (power transducer)	W/cm²	50	40	20
Maximum Intensity of ultrasound impulse (normal transducer)	W/cm²	4	3	2
Average Intensity (power transducer)	W/cm²	0.05	0.04	0.02
Average Intensity (normal transducer)	W/cm²	0.004	0.003	0.003

The average intensity has been calculated for a pulse length of 5×10⁻⁶ second and a pulse rate of 200 per second, Böhme (21)

mann (15) If the fluid contains dissolved gas the bubbles also contain gas — a *phenomenon known as pseudocavitation.* Genuine cavitation implies that the fluid be completely gasfree. The destructive effects of ultrasound on simple cellular organisms have been shown to be often combined with pseudocavitation. Cavitation has been seen in frogs when placed in an ultrasound beam at a frequency of 1 Mc/s when the intensity reaches 17—20 watts/sq cm (50)

Lehmann & Herrick (103) by irradiating white mice produced petechiae of the peritoneum which they considered to be due to cavitation. Irradiation of the same intensity but carried out with increased external pressure caused no petechiae, presumed to be due to prevention of cavitation by the raised external pressure. 2 minutes continuous exposure to 1 watt/sq cm at normal pressure resulted in no petechiae, while 2 watts/sq cm for 2 minutes resulted in petechiae in 45 % of the animals. 1 Mc/s was used throughout. If 0.175 Mc/s is used instead however the same intensities cause more damage. The capacity to produce cavitation increases with diminishing frequency down to a limit of about 0.4 Mc/s.

2. *Heating effect.* Quite apart from the mechanical effects described above, ultrasound also has a heating effect, due to absorption of sound energy and conversion to heat. The energy absorbed per unit volume per second at point x_0 can be expressed as $\alpha\ I_{(x_0)}$, α being the intensity absorption coefficient (see page 12) Several investigations have shown that ultrasound, in the doses used therapeutically has a thermic effect on tissues and organs (40 68, 97 99 100 134 135, 136, 139) Pohlman et al. (127) investigated the temperature rise in the tissues of the human gluteal region in vivo following 20 seconds irradiation at 4 watts/sq. cm and 0.8 Mc/s. At a depth of 2—5 mm from the surface the rise was 5—6 and at 2.5 cm and 3.5 cm the rise was 3.7 and 2.7 respectively With increased exposure durations no further increases in temperature followed, this state of equilibrium being in part due to the cooling effect of the circulation. If dead tissues were irradiated equilibrium was reached at a significantly higher temperature.

It is characteristic of ultrasound that it causes selective heating of different tissues. This depends on the wide variations in these tissues coefficient of sound absorption. See table 2, page 12. Rosenberger (129) found that in animals, when the sciatic nerve region is exposed to ultrasound, the nerve itself became hotter than the over and underlying soft tissues. Bone, which has a very high coefficient of sound absorption similarly becomes considerably warmer than the surrounding muscle and fat, a phenomenon which has received the attention of, among others, Nelson, Herrick & Krusen (115) and Herrick (68) In general it can be said that ultrasound s heating effect is greatest in bone and connective tissue, and least in blood and fat.

Pätzold & Born (128) found a selective rise in temperature at tendinous and myofascial interfaces, and *Horvath (75) observed marked temperature* rises at interfaces between va-

Chapter II

ULTRASOUND AS A DIAGNOSTIC TOOL.

Ultrasound has been used for diagnostic purposes in medicine in many different ways, and it is proposed now to give a brief review of the developments within this field.

The first attempt to use ultrasound as an aid to diagnosis was reported in 1942 by Dussik (28) He used the so called transmission method, somewhat similar to the way in which x-rays are used in conventional radiology The region to be examined (in this case the skull) was exposed from one side, point by point, to a beam of parallel ultra sonic rays. These were then recorded as they emerged from the opposite side of the skull, having been subjected to differential absorption by the varying tissues traversed. A composite picture is thus built up and displayed on a cathode ray oscilloscope, the result being referred to as a Hyperphonogram. In this way Dussik (29) and later Ballantine (5) Hüter (85) and others produced pictures which purported to represent the fluid filled ventricular system. Güttner Fiedler & Pätzold (63) however showed in 1952, that the ventricular system was not demonstrable by this method, because of interference from the skull bones. Further they showed that a skull filled with water gave pictures similar to those considered by Dussik & co-workers to represent the ventricular system. Explanation of this paradox was sought in the singular structure and form of the skull bones. Ballantine, Hüter & Bolt (6) after fur ther studies also concluded that the method was valueless. In 1946 Denier (24, 25) described an ultrasonoscope, employing the transmission method, with which he attempted to map out the position of various structures in the body such as the heart, liver and spleen.

Keidel (92) in 1950 used a variation of the transmission method for recording the fluctuations in heart volume occurring during the cardiac cycle. He directed continuous ultrasound through the chest at the level of the heart and recorded the residual intensity after passage through the thorax. He found that the intensity fluctuated synchronously with the heart beat, and this was attributed

Krusen (104) is a heating effect, accentuated by the multiple interfaces present in the tumour tissue. Burow & Andreewskaja (19 20) could find no other explanation for the selective disintegration of cancer tissue following ultrasound irradiation at 500 watts/sq cm. The selective histological changes in nerve branches within muscles, observed by Herrick et al. (68) following exposure to ultrasound were also attributed to selective heating. The muscle tissue was undamaged.

Fry et al. (48, 49 50) considers that high ultrasound intensities (30—1500 watts/sq. cm) cause irreversible damage of a non thermal nature in nerve cells. Whether this is due to some specific effect or whether it is of a mechanical nature has not been determined.

Dunn (27) by exposing the lumbar region in young mice to high intensity ultrasound has produced motor neuron damage with resulting paralysis of the hindlegs. He considers furthermore that he has shown that these injuries are not a result of heating effects. The existence of a specific effect is disputed by many workers. Hüter et al. (84) in similar experiments produced paralysis of the hindlegs in mice by intermittent exposure of the spinal cord at an intensity of 300 watts/sq cm. 4 pulses of 1 second each over the course of 10 seconds produced paralysis in 95 % of the animals, while 40 pulses of 0.1 second each over 20 seconds resulted in paralysis in only 15 % of the animals. The total energy and the total irradiation time were the same in both cases. This renders unlikely any question of a specific effect and lends support to the heating theory

Bell et al. (12, 4, 2) working with myelinated and unmyelinated nerve tissue have produced so called microlesions (involving sometimes as few as 50 nerve cells) by irradiation with focussed ultrasound of 2.7 Mc/s frequency at an intensity of 1700 watts/sq.cm for 0.25 second. By increasing the time of exposure, with the same intensity a lesion can be produced with a cross sectional area 3 to 5 times greater than that of the beam (focus 0.8 mm and frequency 2.7 Mc/s) The authors maintain that only heat can be the cause of this damage in a zone through which the ultrasound did not pass. The possibility of a specific effect is not, however excluded thereby Herrick & co-workers (3) are also among those who consider that these nerve reactions are primarily due to a heating effect.

Ultrasound has a haemolysing effect on erythrocytes suspended in physiological saline solution (98) This phenomenon is most marked at a frequency of 0.3 to 0.6 Mc/s, and falls off with increased viscosity in the fluid. At frequencies of 1 Mc/s and more blood is not haemolysed. The phenomenon does not therefore occur in the living organism with the frequencies used in practice (100 101)

The dosage threshold for injury

Koeppen (95) working with dogs and rabbits, has made a thorough investigation into the effect of ultrasound on various organs, especially the liver spleen and bone marrow According to this author the degree of temperature

In 1953 Hertz & the author began to use the unidimensional method for examination of the heart (A-scope tech nique) In our first publication) (34) it was shown that from the isolated heart preparation echoes could be obtained from the interfaces between the muscular walls and the blood filled cavities, as well as from auricular thrombi. Further it was shown that similar echoes could be obtained on examination of patients, and the heart movements could be recorded as an ultra soundcardiogram. This permitted investigation of dynamic factors, and it was found that certain echo signals which were presumed to arise from the wall of the left atrium altered in character in mitral stenosis.

After further investigations in living subjects it was found that with the ultrasoundcardiogram it was possible to distinguish between pure mitral stenosis and those in which incompetence predominated. Exudative pericarditis and left auricular thrombi could also be demonstrated (31, 72) The method furthermore lent itself to estimation of the degree of stenosis in the mitral ostium (32, 33, 35) Ultrasound cardiogra phy has since been taken up by other workers (37 63 88, 133) who have by and large endorsed the impressions we have gained. Effert (36) who, like ourselves uses the method routinely in selection of cases for operation in mitral stenosis, published in 1959 his experiences with ultrasound car diography in roughly 600 patients, 432 of whom had mitral stenosis.

) The results from these investigations in 1964 are given in chapter VI.

Kikuchi & co-workers (94) who in 1956 reviewed their experiences with the diagnostic use of ultrasound at The Second International Congress on Acoustics, held at Cambridge, Massachusetts, write "When we inspected at the heart apex of the front thoracic wall, we observed a special echo, which oscillated delicately but rapidly to and fro changing the echo intensity and position on the cathoderay screen with synchroni sation to each heart-beat. This echo is doubtless an echo from the heart" The work of these authors relating to other ultrasound applications in medicine will be referred to again on page 20.

Wild et al. (141) who used the Echograph for two-dimensional visualisation of mammary tumours reported in 1957 that they had used the same apparatus to examine an infarction in a heart excised post mortem. Not only the in farct was visualised with the Echograph but also the left coronary artery and the aorta.

Satomura et al. (131 132, 148) have used the ultrasound echo method in an entirely different way In 1956 and 1957 they described a technique utilizing the Doppler effect to obtain information about the movements of the heart. When the continuous beam is transmit ted from the chest wall to the heart and is reflected from the heart struc tures, it undergoes Doppler effect subject to the movements of the heart. When this reflected wave is detected together with the direct wave a beat appears, the frequency f of which is

$$f = 2\mu/\lambda$$

μ = speed of echogiving structure s movement parallel to ultrasonic beam.

which progressively severe and continuous deep boring pain occured. Paul et al. (121) have also studied the effect of ultrasound on muscle and reached similar conclusions to those of Bickford & co-workers.

Fischer (41) exposed white male rabbits to ultrasound at a frequency of 1 Mc/s and an intensity of 1 watt/sq cm and thus demonstrated a temporary enlargement of the vascular space At 4 watts/sq cm intracellular oedema resulted. Gersten et al. (51, 52, 53 55) in experiments on striated frog muscle in vitro, showed that the membrane properties are altered by ultrasound at a frequency of 1 Mc/s and intensities of 0.5—3 watts/sq cm. Gersten (54) considers that this effect is nonthermal, but "occured in restricted experimental situations. One cannot extrapolate to therapeutic non-thermal effects from these studies" Earlier investigations have demonstrated that ultrasound can affect membrane permeability to ions. Thus Lehmann & Biegler (102) have shown that the selective passage of ions across a membrane consisting of frog skin increases during ultrasound irradiation of 0.5—3 watts/sq cm intensity and 1 Mc/s frequency Lehmann attributes this phenomenon to ultrasound's heating effect.

Higashino (73) exposed nerve muscle preparations to 0.6 to 0.9 watt/sq cm at 1 Mc/s for 5 minutes, and subsequently felt able to show that ultra sound had a stimulating action on nerve tissue. This be regarded as a non thermal effect.

Intermittent irradiation or pulsing technique as means of obviating heating effects.

The thermal effects of ultrasound can be reduced by the selection of an appropriate pulsing technique. The apparatus used emits short sound-pulses at precise time intervals (see chapter IV) The product of the number of pulses per unit time and the pulse duration is called the duty factor Herrick (68) found a temperature rise of 12.28 in the bone cortex of the femur in dogs, when exposed to 2 watts at 0.8 Mc/s continuous energy (100 % duty factor) With unchanged duration but only 40 % duty factor the temperature rise was 4.18 with 20 % duty factor 1.98 and with 10 % duty factor only 0.98

In the aforementioned studies Hilter et al. (84) found that by reducing the duty factor from 40 % to 20 % only 15 % of the mice, instead of the previous 40 % suffered paralysis of the hindlegs after irradiation of the spinal cord. In both series of experiments the peak intensity was 300 watts, and the effective exposure time (product of duration and frequency of pulses) constant.

Lehmann (100) has shown that the hyperaemic reaction to ultrasound of 1 Mc/s frequency and 4 watts/sq cm average intensity was *significantly* less when it was pulsed than when it was continuous despite the fact that the local energy of irradiation and hence the local mechanical effect was the same in both cases.

French et al. (45) carried out direct irradiation of the cerebrum in experimental animals (cats and rabbits) using

observation that the rhythmical heart motion could be studied by means of ultrasonic waves.

Ultrasound has furthermore been used in ophthalmology for detecting intra-ocular tumours, ablation of the retina, rupture of the sclera and foreign bodies in the orbit (114, 118, 120 119 117 8, 9 10) Mundt & Hughes as well as Oksala & Lethinen use the uni-dimensional method, while Baum & Greenwood have used the two-dimensional technique.

Donald et al. (26) reported in 1958 that they had used ultrasound for investigation of large intra abdominal masses, including the gravid uterus, pelvic tumours and ascites. They described a scanning mechanism whereby cross-sectional views of the abdomen were obtained. The authors view however was that their findings were still of more academic interest than of practical importance, and they did not feel that they should allow ultrasonic findings to influence their clinical judgment.

Among others who have worked with ultrasound diagnostic methods should be mentioned Beck (11) who has obtained two-dimensional pictures by mechanically scanning an area with a small ultrasonic beam. In this way he obtained satisfactory pictures of the bones of the forearm and hand. Attempts to diagnose gallstones by ultrasound have been renewed by Bannaski & Fischer (7) Hayashi, Kikucki & Uchida (66) have recently reported good results in this sphere. Yamakava (66) with a miniature laparoscopic sound probe has carried out examinations of the abdominal viscera and thereby been able to detect, among other things, the presence position, number and size of gallstones.

Howry et al. (79) have also attempted three-dimensional and stereoscopic observations of body structure by building up two composite pictures taken from two angles 10 apart, and studying them in a stereoviewer

The way in which the human body is built up of many different tissues and structures, often in thin layers, implies that sound reflecting interfaces are frequently found packed closely together Therefore when echo-sounding from the body surface towards the underlying organs and muscles, multiple but uncharacteristic echoes are often obtained. It is as a rule difficult to ascertain precisely from which structures these arise. A step forward has been made by systematically moving the sound generator in relation to the object under examination (scanning) thus producing a two-dimensional picture. The best results are obtained with fluid filled cavities. The eye, being fluid filled, and containing several sharply demarcated structures, appears specially suitable for examination by both the uni and two-dimensional methods.

The cranium and the heart produce only a very few characteristic echoes, which in fact has made possible the development of echoencephalography and ultrasoundcardiography by the uni dimensional method. In the latter cardiac dynamics render the various echo signals easily identifiable, and furthermore, inferences related to dynamic aspects can be derived from investigation results.

soundcardiography and has seen no harmful effects. Sometimes an increase in pulse rate is detected at the beginning of the examination, but the same is sometimes seen during ordinary auscultation. In the great majority of cases simultaneous ECGs were taken and no changes have been seen with the exception of the aforementioned mild tachycardia in a few patients. Hertz has carried out repeated ultrasound cardiography on himself over the last seven years without noticing any untoward effect.

Chapter III

THE EFFECTS OF ULTRASOUND ON TISSUES AND ORGANS IN ANIMALS AND HUMANS.

The literature contains countless reports of the effects of ultrasound on biological tissues. The first such effect was observed in connection with Langevin's construction of an ultrasound generator for underwater communication in 1917. Wood commented that during these original experiments he felt "an almost insupportable pain which gave the impression that the bones were heated" when he held his hand near the transmitter under water [*quoted from* Nelson, Herrick & Krusen (116)]. It was also noticed that fishes died when they swam into the ultrasound beam.

The *first* systematic investigation of the biological effects of ultrasound was carried out by Wood & Loomis (147) in 1924. They produced injuries and death with ultrasound in mice, fishes and frogs, and subsequent examination of these creatures revealed intra-abdominal haemorrhages and erythrocyte destruction. In 1940 Conte & Delorenzi (22) observed that brain and spleen were particularly sensitive to ultrasound.

Following Pohlman's (126) introduction of ultrasound as a therapeutic agent, the method became increasingly widespread during the 40's, especially in Germany, France, Austria and Switzerland. It was prescribed for a wide variety of complaints, but especially for neuralgia, myalgia, arthritis, arthroses and other conditions for which heat was considered beneficial. This treatment form became popular notwithstanding lack of detailed knowledge *as to its effects on human tissues*, and a variety of complications were reported. Buchtala (17) reported attacks of angina pectoris in six of his cases during exposure of the stellate ganglion to ultrasound, subsequent ECGs revealing no pathology. Generalised collapse after 20 minutes high intensity irradiation of the heart area was reported by Henkel (67) (no information as to intensity). Buchtala (17) mentions a case reported at the Ultraschalltagung des Ärztevereins by Hertzog in 1949 involving a patient with bronchial asthma who was treated by ultrasound irradiation (duration and intensity unspe-

part of the latter may be reflected back towards the crystal, which then acts as a microphone for the detection of these echoes, (see Fig 4) If the velocity of sound in the material is known and constant, then the time elapsing between the emission of the sound pulse and the arrival of the echo is a measure of the distance between the crystal and the reflecting boundary The sound generating and receiving equipment is connected to a cathode ray tube CRT Figs. 4 and 5. At each sound pulse the electron beam is started at the left side of the screen and moves to the right along the x-axis at constant speed. When an echo arrives back at the crystal it is converted to an electrical signal, which is then amplified and fed to the y plates of the cathode ray tube. This results in a vertical deflection of the electron beam. The echo signals E_1 and E_2, Fig. 4, are thus seen as vertical deflections on the oscilloscope screen. As each impulse is emitted a vertical signal (henceforth referred to as the emission signal 0) simultaneously appears on the left side of the screen, thus fixing the zero-point in the picture. Since both the sound in the material under examination (providing it is homogeneous) and the electron beam on the oscilloscope screen, move at constant speeds, the tube's x-axis can be calibrated to represent distances between the crystal and reflecting surfaces. In Fig. 4 the echo E_2 is produced by the far surface of the material being examined, while the echo E results from an internal structural flaw F From the interval 0 — E_1 on the oscilloscope screen the actual distance between the crystal

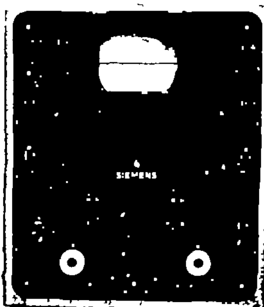


Fig 5. The apparatus from in front showing control panel. Screen of CRT is seen top centre.

C and the flaw F can be easily determined.

All such echo methods require that the sound pulse duration be substantially shorter than the time taken for the sound to reach the reflecting object, necessitating the use of brief pulses of high frequency sound. The equipment we use gives a choice of four different frequencies — 0.5, 1 2.5, and 5 Mc/s, which are selected by a control, 4 on the apparatus at bottom left, Fig 5. Of the two knobs in the middle of the centre panel, 9 10 that to the left is used to vary the impulse duration or impulse width, and that to the right for sideways displacement of the emission signal 0 thereby facilitating accurate reading of measurements. The impulse duration can be varied from 2 to 5×10^{-6} second, which at a sound velocity of 1500 metres/sec. corresponds

the object of eliciting paraesthesias to confirm that the beam was accurately directed. This was the only occasion when such high intensities were used.

In 1950 Nelson, Herrick & Krusen (115, 116) reviewed the medical uses of ultrasound and concluded that ultrasound was too dangerous an agent to be used generally as a therapeutic modality In their paper they discussed the various biological phenomena observed in tissues and test animals. They found during their investigations that irradiation of the thigh in dogs produced a high degree of selective heating of the femur Intensities of 1 and 2 watts/sq cm were used for 90 seconds.

Since the late 1940 s countless biological experiments have been done on organic tissues, and these have in great measure clarified the biological effects of ultrasound, as well as providing information as to how undesireable effects can be avoided.

The mechanics of ultrasound's effect on biological tissues.

1. Mechanical effect In chapter I it was seen that mechanical forces of considerable magnitude may occur in a medium during ultrasonic radiation. Molecular acceleration a, amplitude of vibration A, and maximum speed reached during vibration S are given by the formulae (page 10)

$$a = \omega \sqrt{\frac{2 I 10^7}{\rho v}} \text{ cm/sec.} \qquad (3)$$

$$A = \frac{1}{\omega} \sqrt{\frac{2 I 10^7}{\rho v}} \text{ cm} \qquad (2)$$

$$S = \sqrt{\frac{2 I 10^7}{\rho v}} \text{ cm/sec.} \qquad (1)$$

The sound pressure amplitude P a measure of maximum positive and negative pressure is expressed as follows

$$P = 2 \pi f \rho v A \text{ dynes/sq cm} \qquad (4)$$

In normal therapeutic use of ultrasound a frequency of 1 Mc/s and a maximum intensity of 4 watts/sq cm are the rule. Given that ρ v = 1.6×10^5 g/sq cm sec. (see table 1, page 11) the following values are obtained

Acceleration

$$a = 1.4 \times 10^6 \text{ cm/sec.}^2$$

i. e. more than 1000 times that of gravity which is about 0.98×10^3 cm/sec.^{2}

Amplitude of particles vibration

$$A = \frac{3.6}{10^6} \text{mm} = 0.036 \ \mu$$

Max. speed of particles vibration

$$S = 22.4 \text{ cm/sec.}$$

Sound pressure amplitude

$$P = 3.6 \times 10^6 \text{ dyn/sq. cm} = 3.7 \text{ atm.}$$

All these mechanical quantities change direction with the same frequency as that of the ultrasound, that is to say 10^6 times per second. The sound pressure amplitude is equivalent to half the pressure difference between two points half a wavelength part (here approx. 0.75 mm) along a beam of the intensity in question (here 4 watts/sq cm) The powerful negative pressures which can be evoked with ultrasound give rise to the phenomenon of cavitation, which is seen in experiments involving ultrasound and *fluids*. In hydrodynamics, cavitation refers to the appearance of bubbles in fluids in response to momentary negative pressure. These spaces collapse instantaneously Berg

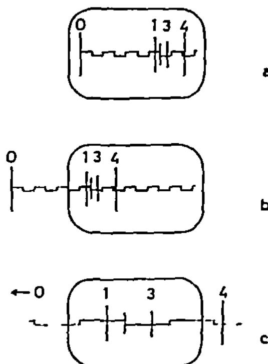


Fig 7 x-axis magnification. 1, 3 and 4 are echo signals. Between 1 and 3 is a second echo signal. a Oscillogram in small scale for orientation purposes. b. Selected part of oscillogram shifted to left hand side of screen. c. Enlargement of selected part by increasing x-axis scanning speed.

distances can be measured with greater accuracy if so desired (see Fig 6) The x-axis magnification has proved of great value during the present work, since the enlarged records obtained show more details and are more suitable for close study

The pulse frequency of the apparatus is 200 per second. The emission signal 0 and echo signals thus appear on the screen at the same frequency

The piezoelectric crystal C is connected by flexible cable to the apparatus. The diameter of the crystal surface is as a rule 12 or 24 mm, thus satisfying the requirements for a well directed beam, at the equipment s operating frequencies (see page 14) In the earlier stages of the work a quartz crystal was used throughout, but latterly a barium titanate crystal has also been used (see page 16)

The construction of the reflectoscope is roughly shown in block diagram Fig. 8. Each time echo ranging commences (i. e. 200 times per sec.) a multivibrator in the control unit M emits a suitable electrical pulse to transmitter T and to sawtooth generator S. The latter the output from which is fed to the x plates of the cathode ray tube CRT instantly returns the electron beam to the zero point on the x-axis, and then deflects it to the right at constant velocity The same electrical pulse, which simultaneously reaches the transmitter causes the latter to produce a signal consisting of a small number of cycles (approx. 2 to 25) of the desired frequency and this in turn is passed on to the crystal C. Here these alternating electrical potentials are converted to mechanical vibrations, which, if the crystal is now pressed against some other material, pass into the latter as a brief pulse of ultrasound.

When an echo arrives back at crystal C the reverse process occurs, and the alternating potentials thus evoked pass from the crystal to the amplifier A. From here, after amplification, the output is fed to the y-plates of the cathode ray tube CRT Thus each echo causes a vertical deflection of the electron beam starting from the point reached along the x-axis at the instant the echo arrives at the crystal. In this way echo signals

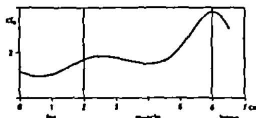


Fig 2. Temperature rise in living tissue. Reprinted by permission from Güttner and Pätzold (64)

rious tissues and other media. This structural heating (135) occurs at abrupt interfaces between zones of differing acoustic impedance (81 83 70) When ultrasound passes from the skin onwards through subcutaneous fat, muscle and bone, it is found that once equilibrium is reached, in conformity with what has been said previously the greatest temperature increase is in the bone and there is considerably less in the muscle and fat. In both bone and muscle the zone of greatest temperature rise is that adjacent to the interface between the two media (64) See Fig. 2. This zone of temperature increase is due partly to the high absorption coefficient of bone, and partly to the extensive reflection of sound from the interface back into the muscle. During the continued transit of sound through the bony structure the intensity falls rapidly because of the high acoustic impedance of this tissue. The heating effect likewise dwindles simultaneously It has also been postulated that this structural heating is in part due to the conversion of longitudinal sound waves into transverse components at this type of abrupt interface. The transverse waves may travel as highly damped shear waves at right angles to the line of propagation of the original longitudinal wave (81 83, 99 70 13, 14)

Structural heating at interfaces increases as the frequency of the sound. Fry (47) has pointed out that even so called homogeneous tissues are far from being uniform throughout and can have many interfaces which result in irregularities in the absorption and reflection of ultrasound energy

3 Some other effects of ultrasound. It has long been known that ultrasound can affect the velocity of chemical reactions. This effect however is seen most commonly in connection with cavitation (60 125) which has never been demonstrated at therapeutic dosage levels (100)

Among the numerous studies and observations on the effects of ultrasound over the last 20 years, no delayed effects (like those, for example following exposure to x-rays) have been seen.

Ultrasound and tissue destruction.

The most pronounced effect of ultrasound on organs and tissues is heating, which can be so intense that the tissue is destroyed. This destruction is also obviously selective. Bell (12) for example found that mice required 15 seconds exposure at 220 watts/sq cm to produce skin necrosis, whereas 12 watts/sq cm was sufficient to produce necrotic foci in the liver parenchyma. Radiant heat can produce the same results providing that the heating effect is similar to that evoked by ultrasound in the tissue concerned. In high doses ultrasound has a destructive effect on sarcoma and cancer cells (74, 74a, 76) and this, according to Lehmann &

Chapter V

RECORDING TECHNIQUE.

The object of examining the heart with ultrasound is to study the movement-patterns of its various structures with the cardiac cycle. To make this possible a method is required for continuous recording of the mobile echo signals. This can be done either by a photographic method, or via one of the channels of a direct writing electrocardiograph.

A. Photographic method.

This was described in 1954 by Hertz and the author (34) In front of the oscilloscope screen is placed a camera, as shown in Fig. 9 Fig 10 is a sketch of the recording arrangements. The lens O focuses an image of the oscilloscope screen onto the film F which is masked by a shield. Across the shield runs a slot S, 0.3 mm wide, arranged so that image from the oscilloscope screen is blocked except for a strip 2—3 mm above the x-axis. The film is wound forwards at a constant speed of 12.4 mm/sec. For this purpose a geared-down Bodine synchronous motor Mo is used, the effect of which is 8 W (Fig. 11) Transmission is by a rubber friction drive D via a worm W and worm wheel S to rubber-clad roller R, which feeds the film F onwards. A subsidiary roller V keeps the film pressed against the driving roller R. This rather complicated set up has been chosen so as to ensure smooth continuous movement of the film. To further ensure this it was found necessary to keep the worm drive W pressed against the wormwheel S at constant pressure by means of a spring T

The film is contained in a cassette C, from which it is pulled out and fed onwards at a constant speed of 12.4 mm/sec. by the above mentioned driving roller R. A motionless echo signal is reproduced on the film as a straight line at a constant distance from the emission signal 0 cf. Fig. 10 An echo signal which moves along the x-axis appears as a curve which corresponds to the movements of the echo giving structure. By means of the x-sweep magnification and axis-shift a limited area can be examined selectively and in detail (see page 36 and Fig. 7 chap-

rise in a tissue determines the degree of damage. 1 watt/sq cm for 2 minutes results in hyperaemia. Histological examination 21 days later revealed no evidence of damage in blood vessels or elsewhere. 2 watts/sq cm for 3 to 5 minutes however produced vascular spasm and tissue ischaemia. Histological examination 21 days later again showed no vascular damage. The irradiation did however cause liver cell damage — maximal 3 days after exposure. By the 21st day regeneration had occurred with capsular thickening. The spleen was also damaged by this dose. At 4 watts/sq cm 2 minutes exposure resulted in circulatory collapse and extensive necrosis subsequently appeared in those parenchymatous organs which had been irradiated.

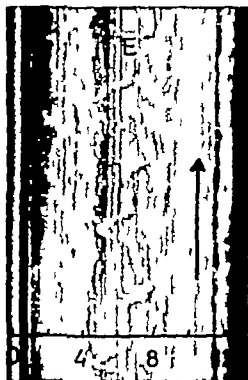
The great susceptibility of nervous tissue to ultrasound was shown in 1942 and 1944 by Lynn et al. (111 112, 113) Herrick (68) irradiated the sciatic nerve in dogs with 2 watts/sq cm at 0.8 Mc/s and found that for a given stimulus the action potential was reduced by 50 % or more. The temperature of the surrounding tissues rose to 48.5—51.6 C. An identical effect on nerve function could be obtained by direct warming to the same temperature. Hüter et al. (85) was able to demonstrate EEG changes in man and animals by exposing the cerebrum to ultrasound of 15 watts/sq cm intensity and 0.8 Mc/s frequency

In the studies of Dunn (27) previously referred to, in which paralyses were produced in mice by irradiation of th spinal cord, estimates were made of among other things, the relationships between exposure time, acoustic intensity and injurious effects. It was thus discovered that at a basal temperature of 20 C, the minimum exposure time required to produce paralysis in 50 % of the animals was 0.8 second at 100 watts/sq cm, and 4 seconds at about 50 watts/sq cm.

Hüter (82) has furthermore elicited pain with ultrasound of 0.8 Mc/s by applying a transmitter to different parts of the hands, arms and legs. The pain was felt at a point below the surface, presumably in the periosteum. At higher intensities pain is felt immediately With continuous irradiation at 2.5 watts/sq cm pain is felt after a delay of 15—20 seconds. Below about 1.8 watts/sq cm pain is not felt however long the exposure is continued. As mentioned on page 24, Buchtala reported that with a frequency of 1 Mc/s paraesthesias are experienced at an intensity of 1 watt/sq. cm.

The effect of ultrasound on blood flow in striated muscle has been studied by a number of research groups (16, 121 87 1) Bickford & Duff (16) have investigated temperature and blood flow changes in the forearm (plethysmographic method) following 10—15 minutes exposure to various intensities of ultrasound at 0.8 Mc/s. A consistent, sustained increase in flow occured with intensities of 3—3.5 watts/sq. cm. At 2 watts/sq. cm this occured in only half the cases examined. This increased blood flow was attributed by the author to a vasodilatation in the muscle, secondary to a local thermogenic effect. Bickford & Duff point out that 3—3.5 watts/sq. cm was found to be the limit of tolerance in almost every subject, beyond

Fig 11



a



b

diagnostic equipment which worked at 1000 impulses/second, with a duty factor of 1/1000 a frequency of 15 Mc/s, and a peak intensity of 70 watts/sq cm. The exposure time was 15—20 minutes. Subsequently the animals showed no ill effects whatever Moreover histological examinations of the brain at suitable intervals during the following weeks showed no sign of injury One of the authors exposed his own arm to irradiation for 30 minutes with the same apparatus. No feelings of warmth or pain were experienced. No late sequelae have appeared (142)

Thus the pulsing method provides a way of minimising thermal effects and of eliminating the risk of injury even with very high intensities.

Summary of ultrasound's effects on tissues and organs at frequencies of 0.8—3 Mc/s.

1. It is now generally accepted that exposure of living tissues to ultrasound at intensities of 0.5—3 watts/sq cm as used in physical therapy produces effects which are mainly thermal in origin. Whether injuries are produced by non-thermal effects at these intensities, is still a matter for speculation.

2. By intermittent or pulsed irradiation the effects of ultrasound can be reduced, so that high intensities have no demonstrable injurious results and produce only a sensation of warmth, provided that the applied energy does *not exceed 1 watt/sq cm.*

3. In applying irradiation to muscle in man the threshold value for increased blood perfusion in that muscle, brought about by the thermal effect, is 10—15 minutes at 2 watts/sq cm.

4. Exposure of the precordium for 6 minutes with 3 watts/sq cm at 1 Mc/s and for 10 minutes with 4 watts/sq cm at 0.8 Mc/s has produced no damage or functional injury

5. The *threshold value* for pain production is 1 watt/sq cm at 1 Mc/s or 1.8 watts/sq cm at 0.8 Mc/s, with continuous irradiation.

The risk of injury in ultrasound-cardiography

The equipment used by the author (Ultraschall-Impulsgerät II, Siemens Reiniger Werke) emits 200 pulses per second with a maximal impulse duration of 5.10 $^{-6}$ second. The total transmitting time per second thus being 1/1000 second. The duty factor is therefore 1/1000. In the more modern power transducers, the peak intensities are 80 40 and 20 watts/sq cm at 1, 2.5 and 5 Mc/s respectively which, with a duty factor of 1/1000 gives mean intensities of 0 08, 0 04 and 0.02 watts/sq cm. For ordinary transducers the average intensity is 0.004 at 1 Mc/s and 0.003 watts/sq cm at 2.5 and 5 Mc/s. See table 4 page 15.

It will be readily apparent therefore that the intensities used in ultrasound-cardiography do not exceed 10 % of those required to produce sensations of warmth in man. At these intensities and at the frequencies in question no ill effects whatsoever have been observed in human subjects.

Since October 1953 the author has carried out 2500 examinations with ultra

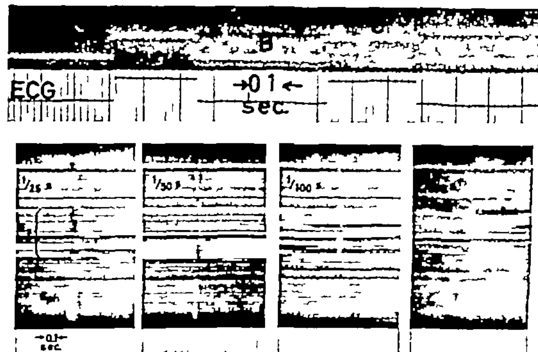


Fig. 14. A method of testing the ability of the photographic technique to record the movements of echo signals and ECG signals on the oscilloscope screen. Time intervals 0.10 sec. between thick lines, 0.02 sec. between thin lines. Paper-speed 100 mm/sec. Above: The ECG machine's response to a test of 1 mV recorded both on the ultrasound film-track, F and by the normal method, ECG. A and C on the ultrasound film indicate F's response to two tests. B indicates F's zero position between tests. A and C are 3.0 and barely 3.5 mm longer respectively than the simultaneously recorded interruptions in F. B is 3.0 mm longer than the interval between A and C. The overlap at each shift in position is thus not in excess of 1.75 mm, i.e. 0.0175 sec. Below: Echo signals recorded during alterations of the distance to the echo-giving structure occupying 1/25, 1/50, 1/100 and 1/200 sec, respectively. The layout was basically the same as that used for testing the direct-recording equipment, as described on pages 46 and 47. E_s = echo signal from the shutter. E_{ph} = echo signal from the photocell. Ph = signal from the mirror galvanometer which is connected to the photocell via one of the channels of a Klinik ECG machine. When the shutter is open for 1/25 and 1/50 sec there is a clear interruption in the echo signal E_s. When the shutter is open for 1/100 sec E_s becomes weaker but does not disappear entirely. When the shutter is open for 1/200 sec there is no interruption in E_s. It can be seen from the tracing that an echo signal with a duration of 1/100 sec can be recorded on the film. Because of overlap, a distinct tracing of movements is not obtained in the case of events having a duration of 1/100 sec. Events lasting 1/50 sec or more give rise to distinct records.

ured at intervals of 0.005 sec. Events having a duration of 0.01 sec. or more can therefore be registered on the oscilloscope screen.

Since the slot width in front of the camera is 0.3 mm and the film speed is 12.4 mm per sec. the resulting film exposure is roughly 0.024 second. Signal

Chapter IV

EQUIPMENT

The apparatus used for the present investigations is an ultrasound reflectoscope (Ultraschall Impulsgerät II) manufactured by Siemens Reiniger Werke, Erlangen, Germany Fig 3 This equipment, which is designed primarily for echo-ranging, is used in industry for nondestructive detection of flaws in materials. It works in the following way Brief ultrasound impulses are generated by an electrically excited quartz

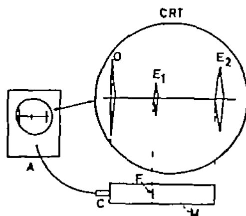


Fig. 4. Flaw detection with ultrasound. C = sound generating and receiving crystal pplied to M = material under investigation. F = flaw CRT = cathode ray tube with resulting pattern to the same scale as test object. 0 — emission signal. E = echo from the flaw E_2 = echo from surface at opposite end of M.

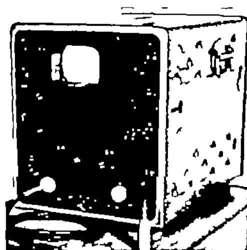


Fig 3. Ultrasonic reflectoscope. Front left crystal connected by cable to reflectoscope. Front right test plug (cf. page 41)

or barium titanate crystal. These pulses are then delivered to the material under investigation by pressing the disc-shaped crystal C directly against the surface of the material M, Fig. 4. A thin film of oil between the two opposed surfaces secures good acoustical contact. If a boundary zone within the material is impinged upon by the sound pulse,

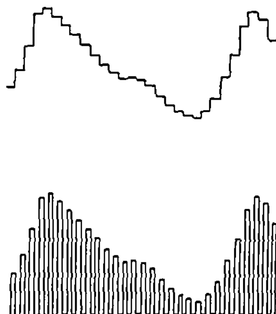


Fig 16. Direct recording (schematised) Above, continuous method as in Fig. 15, lower tracing. Below discontinuous method wherein tracing returns to zero-line between each measurement point. Reprinted by permission of Effert, Hertz & Böhme (29)

cording the result on a direct writing recorder for example an Elema Mingograf recorder the upper frequency limit of which is 1000 c/s. In order to do this the transit time value must be converted to an electrical potential which is preserved for 5 milliseconds.

This conversion can be made by employing the principle of short time measurement, using a condensor discharge. The condensor previously charged to a predetermined level is made to discharge with a constant current during each measuring cycle so that the fall in potential is proportional to the transit time The residual charge remains constant until the next measuring cycle and is in the meantime recorded by the Mingograf recorder In this way the resulting tracing forms a record of the echo-giving structure's movements relative to the sound generator

The technical arrangements are outlined schematically in Fig. 15 which shows a sequence of two consecutive measuring cycles, together with the circuit diagram. At a predetermined interval *after the emission of the sound* pulse the electron beam begins to sweep from left to right across the oscilloscope screen (see 'x-sweep magnification page 36) At this instant, the thyratron V_1 fires, charging the condensor C_m to a potential U_0 in a fraction of the transit time T The condensor discharges via the pentode V_2, the anode current of which is for practical purposes independant of the anode potential, or in other words, the condenser potential. Thus the discharge current is practically constant and the potential U therefore falls linearly during transit time T The next echo signal arriving after the charging of the condensor throws over a bi-stable multivibrator circuit, which in turn makes the grid of the pentode V_2 negative thus cutting off this valve. The charge on the condensor then remains at the value U_0 $(1-T/T_0)$ *which is passed on to* the Mingograf oscillograph by a cathode-*follower circuit. This sequence is re*peated 200 times per sec. and the Mingograf thus records the potentials at this rate. The peaks in potential are not reproduced because the apparatus has low transient sensitivity and an even tracing therefore results, Fig. 16 above

If, at the midpoint between consecutive measuring cycles, the value U is permitted to drop by completely dis-

with an impulse width of 3 to 7.5 mm. The two knobs, 1 2, above and to the left regulate illumination and focus on the oscilloscope screen, and the third control, 3, on the lefts is for adjusting the intensity and amplitude of the outgoing impulse. The degree of echo amplification and thus the size of the echo signal as seen on the screen can be varied by the knob 8 low down on the right hand side.

By means of a switch, 5, (top right) and a fine adjustment control, 6, (second from top, right) the equipment can be set for the varying thicknesses of material to be examined (range — 0.8 to 200 cm at sound velocity 1500 m/s) so allowing the entire width of the scan to be utilised in each case. The control, 7 on the right side, third from top, is used for time calibration, by means of which the zero line or x-axis is divided into equal

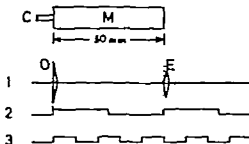


Fig 6. Scale for measuring of distances. O=crystal, M=homogeneous medium of known length (in figure 50 mm) Interval 0—E on screen's x-axis represents the time taken for sound to travel through M and back again. The square-wave marker can be adjusted to produce a single wave between 0 and E. If more accurate measurements are required the square waves can be subdivided by adjustment of a control switch, so as to be 1/2, 1/5, 1/20 or 1/50 the length of the original 0—E. 1. 0—E is 50 mm. 2. The length of each square wave is 25 mm. 3 The length of each square wave is 10 mm

time intervals by square waves of similar length which appear on the screen, Fig 6. The length of these square waves can be adjusted so as to represent the time taken for the sound to travel a given distance through the medium in question. This control allows a choice of five settings, demarcating the distance 0—E into intervals of 1 2 5, 20 or 50 arbitrary units. Thus without knowing the speed of sound in the test medium the equipment can be adjusted to produce the desired number of square waves on the screen between the time of emergence of the sound pulse and the arrival of the echo from the opposite end of a homogeneous medium.

The apparatus also has a special device which permits the enlargement of a limited area of the oscillogram, and thus makes possible a more detailed inspection of this portion. This x-axis magnification enlarges the picture only in the plane of the x-axis, and is brought about by increasing the scanning speed of the electron beam with regard to x-deflection. Simultaneously the start of the x-sweep is delayed electronically after the emission of the sound pulse, to such an extent that only the desired events are shown on the screen at the increased scanning speed. A knob on the right hand panel is used to shift that part of the oscillogram in which one is interested to the left side of the screen, see Figs. 7a and 7b. With the two uppermost controls, 5, 6, on the right side the working range of the equipment is then reduced, thus producing an enlarged picture of the relevant zone for detailed inspection, Fig. 7c. By altering the frequency of the square wave marker the

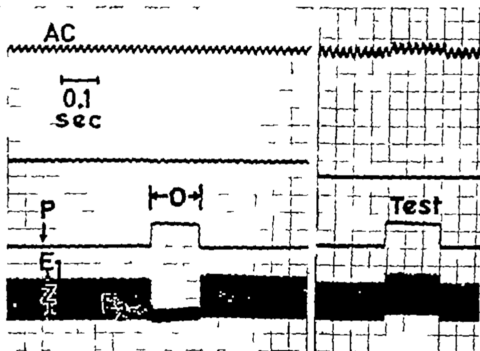


Fig. 19. Testing for response-lag in direct-writing method. See text. P = signal from photoelectric cell. E_1 = echo signals from surface of closed camera shutter. E_2 = echo signals from a surface 2 cm behind shutter (photoelectric cell). O = duration of photocell's exposure to light = duration of shutter opening. Z = zero-line. Test = testing with 1 mV. AC = alternating current interference, 50 cycles/sec. Time marking 0.05 sec. between thick lines, 0.01 sec. between thin lines.

Testing of the direct recording equipment.

The following experiment confirms that the performance of the apparatus meets the above requirements. The ultra sound crystal of the reflectoscope is *placed approx. 2 cm in front of the* aperture of the diaphragm-type shutter of a camera. A photoelectric cell is placed in a light proof box behind the shutter and connected to one of the channels of the Mingograf recorder. Echo signals can now be obtained from the surface of the closed shutter. Opening the shutter however causes light to impinge on the photocell, producing a deflection on the Mingograf record, and the echo signals now no longer originate from the shutter but from the photoelectric cell some centimetres behind the same. That this experiment can be carried out in air is made possible by the use of a more sensitive crystal. The frequency used is 1 Mc/s, and the impulse frequency is, as usual, 200/sec, that is to say the measuring cycles occur at 0.005 second intervals. The ultrasound apparatus is connected to a Mingograf in the usual way through the above described transit time — voltage conversion apparatus. From Fig. 19, which illustrates such

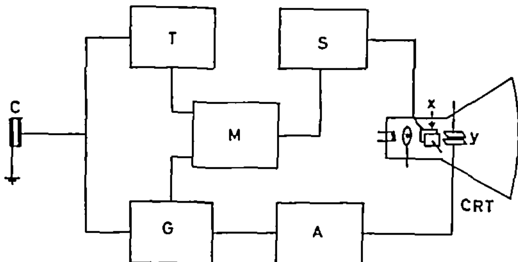


Fig 8. Block diagram of reflectoscope [after Hertz (71)] C = crystal, T = transmitter G = gate, M = multivibrator in control unit, S = sawtooth generator A = amplifier CRT = cathode ray tube, x = horizontal deflecting plates, y = vertical deflecting plates.

E and E_2 are displayed on the screen, Fig. 4. The time marker producing the square wave signals (see page 35 and Fig. 6) is also connected to the y plates in the cathode ray tube.

In order to protect the amplifier from high AC-voltages originating from the transmitter at the beginning of each operating cycle a gate G is interposed between the crystal and the amplifier input. This gate is closed by an impulse from the control unit M simultaneously with the activation of the transmitter If a small leak through the closed gate is arranged, the transmitter's impulse, much reduced in scale, is also seen on the oscilloscope screen. This permits precise definition of the emission signal 0 on the x-axis, Fig. 4.

Our investigations were all carried out initially with disc shaped 12 mm diameter quartz crystals which were supplied with the apparatus as standard equipment. With such crystals an echo could almost always be obtained from the posterior wall of the heart. Mitral valve action, subsequently to be described, could as a rule only be recorded in patients with enlarged hearts. In collaboration with Siemens & Halske A. G., Germany successively improved transducers were evolved, and these have been of prime importance in the progress of this work. With these improved transducers the action of the mitral valve cusps can be recorded in practically every case. However it is still sometimes impossible to obtain such recordings in patients with advanced emphysema, in the very obese and in those with dislocation of the heart to the right. The transducers used at present are disc shaped, have a diameter of 12 mm, and a maximal impulse intensity of from 40 to 80 watts/sq cm. For further details see page 16 and table 4.

Fig 21. Testing time response by checking distance to echo giving structure during 1/200 sec. Time marking· 0.05 sec. between thick lines, 0 01 sec. between thin lines E_1 = echo signals from surface of closed camera shutter E_2 = echo signals from a surface 2 cm behind shutter (photoelectric cell) P = signal from photoelectri cell. AC = alternating current interference, 50 cycles/sec. Z = zero-line. Duration of shutter opening is 1/200 sec in which time apparatu carries out 1 measuring cycle.



Fig 22 Routine ultrasoundcardiogram recording The crystal for generating and detecting ultrasound is applied to the third left intercostal space

electrocardiograph a amplifier it can be arranged that 1 cm of movement by the echo-giving structure is represented by 1 cm of amplitude on the paper

Further details of the directwriting method.

ECG phonogram, and sometimes pressure tracings are used as references in the direct writing method. Providing that the various channels are function ing correctly in accordance with the

Fig 9. Camera placed in front of oscilloscope screen for continuous photographic recording

ter IV) Fig. 12 a shows a small-scale picture for orientation purposes, and Fig. 12 b shows magnification of a selected part of this. The pictures are turned 90 and inspected horizontally so that time is read off on the abscissa and movement amplitudes along the ordinate.

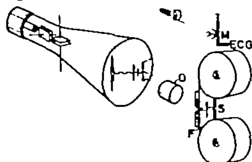


Fig. 10. Arrangements for continuous photographic recording of mobile echo signals on the screen. Film F passes slot S at constant speed. The echo signal is reproduced on the film by lens O M = oscilloscope mirror of galvanometer ECG = leads to electrocardiograph machine. A non-mobil echo signal gives rise to a straight line on the film, whereas a mobile signal gives rise to corresponding fluctuations in the tracing

ECG-recording

The electrocardiogram can be recorded on the film simultaneously with the ultrasound tracing (Fig. 10) This is done by placing, above the camera, a mirror galvanometer which is connected to one of the channels of an electrocardiograph machine with optical recording facilities (Klinik, Elema)

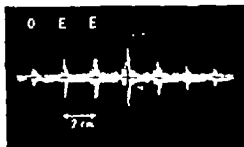


Fig 13 Calibration of distant scale with 'test plug' O = emission signal. E = echo signals Interval between each echo signal represents sound's passage through 2 cm blood and back again to starting point.

The oscilloscope mirror M of the gal vanometer is adjusted so that the reflected light beam produces a verti cal line on the CRT screen at the same level as the echo signals (cf Fig. 10) Pictures are produced from the ultra sound film to the same scale as the simultaneously recorded ECG on the electrocardiograph machine. The time markings on the electrocardiogram thus also apply to the curves on the film i. e. the ultrasoundcardiogram. In the Elinik ECG machine used in this study the paper is advanced by a synchronous motor The machine also has a device which marks off time intervals of 0.02

Fig 11. The photographi recording equipment. Left. Mo=motor D=rubber friction drive. W = worm drive S = worm wheel. T = spring for pressing the worm drive W against the worm wheel. Right R=driving roller F = film. V = roller C = cassette for film.

Fig 12 a. Small scale picture. b. Magnification of the area adjacent to and including echo signal E to permit detailed study of the movement pattern. Arrow indicates direction of film movement.

second on the tracing Paper speeds of 40 or 100 mm/sec. are available.

The echo giving structure s movement amplitudes can be read off vertically from the picture. This is best done by reference to a scale obtained by means of a so called 'test' plug'

The test plug

This has been described by Effert, Hertz & Böhme (39) and it is a means of checking the calibration of the apparatus quickly and easily It consists of a piece of aluminium of suitable length and cylindrical shape, with a piezoelectric crystal attached to one end (cf. Fig 3, page 33) The length has in this case been chosen so that the time taken for the sound to travel from the crystal to the opposite end and back is exactly the same as that taken to traverse 2 cm of blood in each di rection. This test plug can be connected to the apparatus by a special input in stead of the ordinary crystal, whereupon a large number of echoes are seen on the CRT screen Fig. 13. These are due to sound impulses repeatedly bounc ing back and forth between the crystal and the other end of the test plug. There is thus a constant distance between these echoes representing 2 cm of blood, and thereby the inbuilt square-wave marker in the apparatus can be calibrated.

Testing of the photographic method.

The impulse frequency of the ultra sound apparatus is 200 per sec. implying that the distance between the crystal and the echo-giving structure is meas-



Fig. 23. Quartz-crystal applied to isolated human heart. Crystal frequency 2.5 Mc/s.

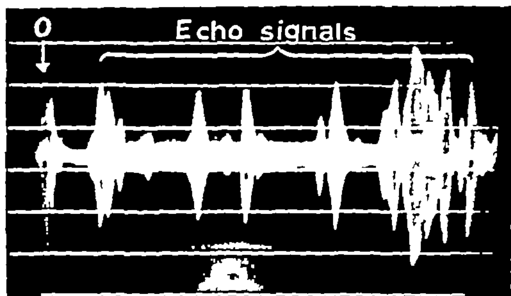


Fig. 24. Echogram obtained on the CRT screen by the arrangement shown in Fig. 23. 0 = emission signal.

deflections of 0.024 second or less are too rapid to be recordable but cause instead a certain degree of blurring in the tracing

In Fig. 14 the photographic method s potential for capturing rapid signal movements on the screen is demonstrat ed. Above is shown the ECG machine s response to a test of 1mV recorded both on the *ultrasound film-track (F) and* by the normal method (ECG) On shift ing position the ECG signal is sharply defined, while signal F ends and begins indistinctly These blurred parts over lap each other to an extent which is partly dependant upon the width of the *slot in front of the camera.* By means of testing the line F has been divided into three distinct parts A, B and C, each having a duration not exceeding the corresponding gaps by more than 0.035 sec. The overlap at each shift in position thus corresponds to 0.0175 sec. This implies that with this record ing technique, events on the oscillo-scope screen having a duration of 0.02 sec or more can be recorded on the film.

Below in Fig 14 are shown recordings of echo signals during alterations of the distance to the echo-giving structure occupying 1/25, 1/50 1/100 and 1/200 sec. Movements lasting 1/50 sec or more give rise to distinct records.

The apparent discrepancy between this figure and the calculated value 0.024 *is due to* the minimum time-requirement for response of the film.

B. The direct-writing method.

Direct recording of the ultrasound car diogram via an electrocardiograph can be

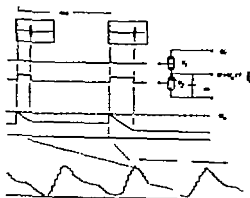


Fig 15. Schematic explanation of the "transit time — voltage conversion ppa ratus. V_1 thyratron for charging the condensor C_m V_2 discharging tube for C_m T and T_2 two consecutive different transit times (following each other) T_e discharge time of the condensor C_m U_e maximum voltage and U residual voltage after discharge of the condensor C_m The lower curve shows the condensor voltage U as *composed from numerous consecutive measurements,* which gives the UCG-curve. Reprinted by permission from *Effert,* Hertz & Böhme (39)

carried out by the method described by Effert, Hertz & Böhme in 1959 (39) In ultrasound cardiography as previously described, one measures the time required by the sound impulse to travel from the sound generator to the reflecting structure in the heart and back again. This so called transit time is of the order of 10- — 10^{-4} sec. and is too brief to be recordable by the normal *clinical electrocardiograph machines* which have an upper frequency limit of at most, *1000 c/s. The following* solution has therefore been devised Since the ultrasound apparatus carries out its measuring cycles 200 times/sec, i. e. once every 5 milliseconds, the intervals between each can be employed for re-

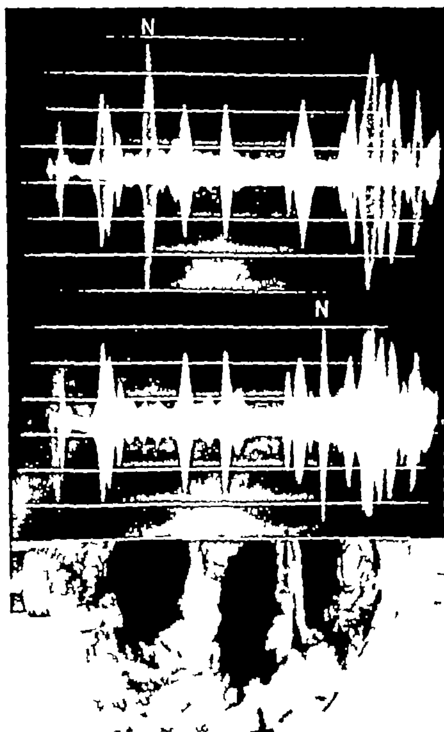


Fig 27 Needl echo signal N appeared when needle was d pped into the left ven tricle pper echogram) and the right atri m (low echogram)

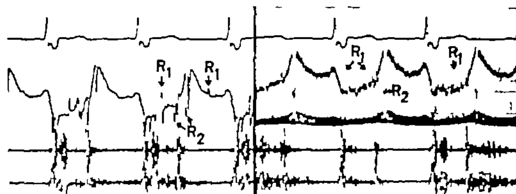


Fig 17 a. Tracing produced by continuous recording method. b. Tracing produced by discontinuous recording method. An interference echo signal on the screen, to the left of the signal actually to be recorded, gives rise to the deflections R_1. A fortuitous amplitude drop in the echo signal gives rise t a defect in the tracing. Deflection R_2 is possibly due to echoes emanating from a more distant structure. Interference results in greater deformation with the continuous recording method than with the discontinuous method.

charging the condensor the Mingograf records zero between each U value The tracing thus consists of 200 individual measuring points per second, Fig 16

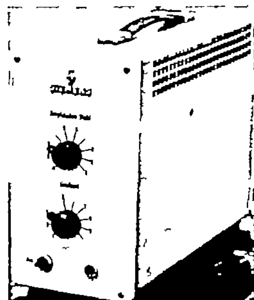


Fig 18. Transit time — voltage conversion apparatus.

below This discontinuous recording method is of advantage compared with the continuous method, since the appearance of the tracing is less disturbed by interference from incidental reflections, Fig. 17 The smaller the ordinate the greater the distance between the echo giving structure and the sound generator

This technique, unlike the photographic method, permits recording of the movements of only a single echo By means of the inbuilt x-sweep magnification device (page 36) the echo under study is shifted to the left hand margin of the oscilloscope screen, and thus triggers the 'transit time — voltage conversion apparatus described above. This apparatus is shown in Fig. 18.

Since in direct recording the ultra sound tracing consists of 200 individual measuring points the upper frequency limit for reproduceable movement sequences is 100 c/s, i. e. two times better than the photographic method.

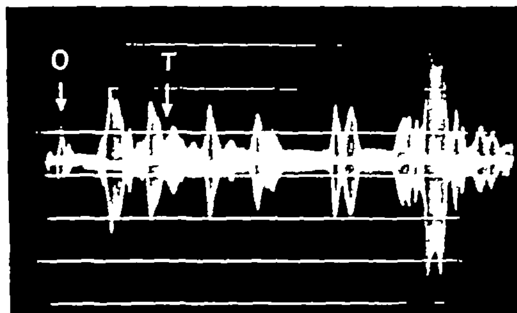


Fig. 29 a. Echogram obtained as in Fig. 28. Comparison with echogram in Fig 24 shows that *multipl echo signals T have appeared in zone corresponding to cavity of* left ventricle.

Fig. 29 b. Apposition of Figs. 28 and 29 a showing correlation between echo signals T and thrombus

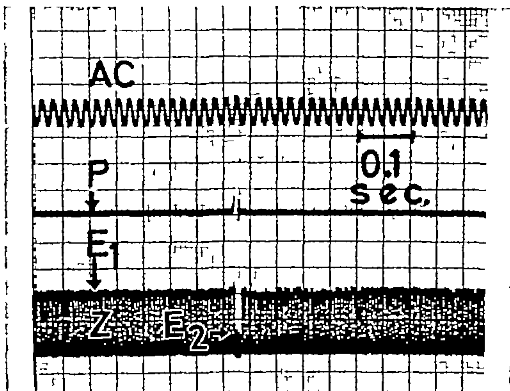


Fig. 20. Testing time response by checking distance to echo giving structure during 1/100 sec. Time marking 0.05 sec. between thick lines, 0.01 sec. between thin lines. E_1 = echo signals from surface of closed camera shutter E_2 = echo signals from a surface 2 cm behind shutter (photoelectri cell) P = 'signal' from photoelectric cell. AC = alternating current interference, 50 cycles/sec. Z = zero-line. Duration of shutter opening is 1/100 sec. in which time apparatus carries out 2 measuring cycles.

a test, it can be seen that there is no measurable time lag between the signal from the photocell and the echo signal.

Figs. 20 and 21 demonstrate the disappearance of the echo signal when the shutter is opened for 1/100 and 1/200 sec., respectively. In the former 2, and in the latter 1, measuring cycles are recorded. The minimum time required for recording a single movement sequence by the direct-writing method is thus only ½ of that required for such a recording by the photographic method.

Calibration of direct recording equipment

The test plug produces echoes on the oscilloscope screen representing intervals of 2 cm. If the scale of echo signals is then moved along the x-axis a deflection equivalent to 2 cm is recorded on the Mingograf paper each time an echo signal passes the left hand margin of the screen. By suitable calibration of the condensor discharge time constant in the 'transit — voltage conversion apparatus and the

3. Detection of thrombi in the heart chambers.
4. Localization of the interfaces between vessel walls and their fluid contents, whether water or heparinised blood. Echoes are obtained from both external and internal surfaces.

tests, there is no measureable lag between the phonocardiogram and ECG tracings.

Using the direct writing Mingograf Elema, paper speeds of 50 and 100 mm per sec. have been used. At the slower speed the fine lines 1 mm apart represent 0 02 sec. and at the faster speed they represent 0 01 sec. These speeds can be checked by comparison with the AC mains interference on the tracing. In Lund the mains AC frequency is 50 cycles/sec with a maximum deviation of plus or minus 0.5 ~

The method of applying the crystal to the precordium of the patient is illustrated in Fig 22.

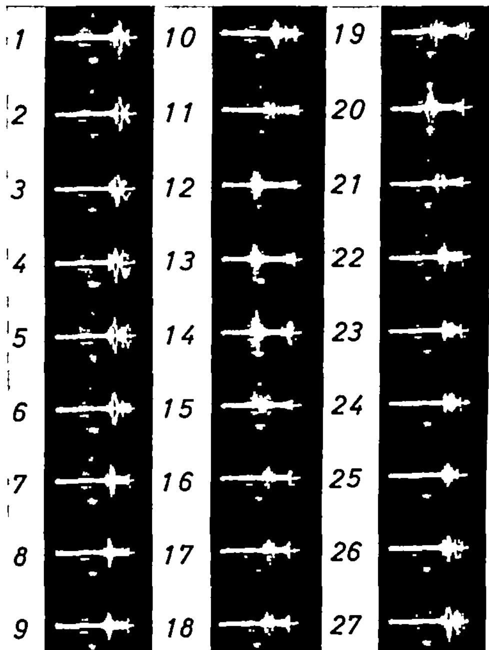


Fig. 32. Filming of echo signal's movements on screen. Film speed 24 frames per sec. Enlarged scale along x-axis. In pictures 1 and 2 the echoes are grouped together on the right side of the screen. From picture 3 onwards the echo on the left starts to move towards th left t first slowly the from pictures 11 to 13, more quickly From pictures 15 to 26 the echo signal returns to its original position. In picture 20 however an incidental deflection to the left can be seen.

Chapter VI

ECHOGRAMS FROM THE ISOLATED HEART THROMBI AND VESSEL WALLS

The essential pre-requisite for ultra soundcardiography is that the blood/heart wall interface reflects sound to such an extent, that it can be detected and recorded. Since the acoustic impedance for muscle is $1\cdot63 \times 10$ and for blood (and water) 1.49×10 gr/sq cm s (see table 1, page 11) the reflexion index R is only about 1/500 (see formula 5 page 11) It was, therefore, exceedingly doubtful, whether it would prove possible to record echoes from these interfaces. For this reason Hertz and the author (34) began in 1953 to investigate the possibility of recording echoes from the isolated heart. Fig. 23 originates from one of these experiments. A transected human heart is seen from above. From left to right are the left ventricle, right ventricle and right atrium. The cavities of these are filled with water and the sound-generating quartz crystal is fixed against the exterior of the left ventricle, so that the sound beam passes through the cavities just below the surface of the water The frequency used is 2.5 Mc/s, and therefore the extent of the near zone is 60 mm and the angle of divergence is 3.5 (see table 3 and text page 14) The distance travelled by the beam through the preparation is 90 mm and therefore by the time it emerges, its cross sectional area is almost doubled. It became apparent that echo signals were easily obtained. Fig. 24 shows the echogram as displayed on the oscilloscope screen. A multiplicity of echoes are seen, but correlation of a given echo with the appropriate heart wall is not obvious at a glance. The pictures are reproduced however so that each division on the scale on the oscilloscope screen corresponds to 1 cm on the scale to right in Fig. 25. By suitably bisecting the two pictures and placing the cut edges together the significance of the echo signals, and their interpretation in terms of heart structure at once become apparent, Fig 25. An echo arises when the sound passes from heart wall into water and vice versa. Thus, provided that each interface gives rise to no more than one echo, then the thickness of the heart wall can be measured. See for exampl the interventricular septum in Fig 25.

Curvatures and irregularities in the

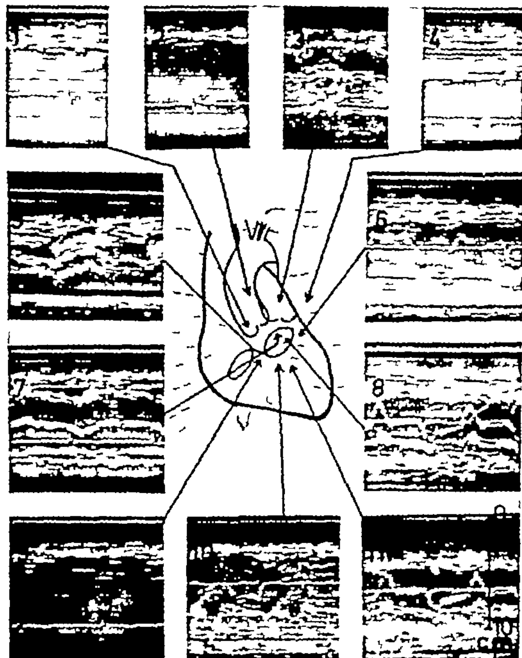


Fig 34. Echograms obtained from different parts of the precordium and adjacent areas. Curves 1, 2 and 9 show recordings made with the crystal applied to the sternum. Curve 4 shows echo-ranging beyond the precordium in the 2nd left interspace. Curve 3 shows recording from the 2nd left interspace over the pulmonary artery. Curves 5 and 7 show recordings made with the crystal applied to 3rd left interspace and directed 10 to 15° medially. Greatest range of movement is seen in the echograms taken from 3rd and 4th left interspace, curves 6, 8 and 11.

Fig 25. Figs. 23 and 24 pposed, rendering pparent the correlation between echo signals and heart walls.

heart wall cause some break-up of echo signals, since at these points the distance quartz crystal — reflecting boundary is not constant over the entire area of the beam. The complex echo signal seen at the place where the sound beam, after traversing the heart, strikes the opposite heart wall is probably due to the highly convex heart form at this point. Similar fractionation is seen at the interface between the left ventricular wall and its cavity. This *splitting of multiple*, partially confluent (but with distinct peaks) echoes is due to interference, as was pointed out by Effert (36). If, between two waves reflected from different parts of the heart wall, the phase shift, t, reaches half a wavelength, then complete break-up will occur as a result of interference. If the shift is a whole wavelength then summation of echoes occurs with a corresponding increase in signal amplitude, see Fig 26. On the other hand, the wall between the right

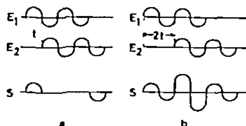


Fig 26. Interference between two echoes arising from different parts of the same interface. a. The time-lag t between E_1 and E_2 is half a wavelength, with consequent splitting of the echo signal S. b. The time-lag between E_1 and E_2 is 2t, that is to say one wavelength, resulting in summation with increased amplitude in echo signal S.

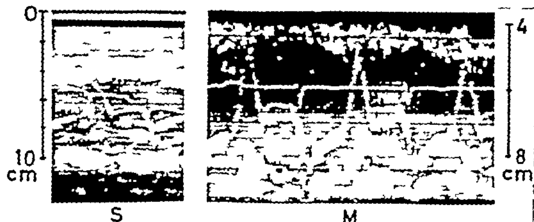


Fig 37 An ultrasound tracing recorded from the third left interspace. The echo signal has a quick movement of 2 cm amplitude.

ed which has a quick characteristic movement of about 2 cm amplitude. This signal's relationship to the emission sig nal indicates that the structure responsible for the echo is some 6—8 cm distant from the anterior chest wall. See Fig. 37 When the present work was begun in 1953 it was only occasionaly possible to record this particular echo whereas now with improved technique it presents no difficulties, except in cases of advanced emphysema or when there is dislocation of the heart to the right. Often, an echo signal of identical appearance can be obtained in the fourth left interspace sometimes it is necessary to direct the beam somewhat upwards. This echo signal has a motion sequence which can be correlated to the pressure variations in the left atrium. Fig. 1 part II.

When the tracing from the third left interspace was first described by Hertz and the author (34) we presumed that is was derived from the anterior wall of the left atrium. Effert et al. 1957 (38) as well as Jacobi et al 1958 (88) Gässler et al. 1958 (65) and Schmitt et al. 1960 (133) had come to the same conclusion. However no satisfactory proof for this assumption was given at that time.

CONCLUSIONS.

The pulsating echo signals are obtained only when the ultrasound beam is aimed at the heart, and furthermore clear correlation can be demonstrated between the movement sequence of these signals and the activity of the heart, as recorded by ECG This points to the heart as being the source of these echoes [Edler & Hertz 1954 (34)] Continuous recording of these signals produces a tracing referred to as an ultrasound cardiogram, UCG We have shown, as described on page 51 chapter VI, that blood/heart wall interfaces reflect ultra sound, and one is therefore justified in assuming that the signals in question arise at least partly from such an inter face.

The posteriorly-arising echo signal, earlier referred to as being recordable



Fig. 23. A thrombus placed in left ventricle of heart-preparation.

atrium and right ventricle, which has been artificially stretched so as to lie precisely perpendicular to the ultrasonic beam, gives rise to sharp echo signals. Naturally the height and the width of the echo signals vary very much if the direction of the sound beam is changed. The experiments described here were done with water so that the shape of the heart chambers under the water surface can be seen on the photographs. In later experiments the heart chambers were filled with heparinised blood, but the results obtained were exactly the same as those found with water

To check that the correlation between the heart walls and the echo signals on the CRT screen given above was correct, the following experiment was performed. An injection needle ca. 0.5 mm thick was dipped from above into one of the heart chambers shown in Fig. 23 in such a way that it crossed the axis of the ultrasonic beam. This resulted in an additional echo signal on the CRT screen from reflection at the needle. The echograms in Fig. 27 were recorded with the needle placed in the left ventricle (above) and in the right atrium (below) respectively. As can be seen from the echograms, the echo signal, N due to the needle always shows up between the echo signals from the walls of the heart chamber into which the needle was dipped in each case. By moving the needle along the axis of the ultrasonic beam from one wall to the other in the heart chamber the needle echo signal could be seen moving between the echo signals from the respective walls.

In 1959 Effert (36, 37) carried out



Fig 30 T right is seen calf's pulmonary artery placed in water Above the artery crystal C. To left of picture, echogram. 0 = emission signal. E = echo signals corresponding to vessel wall.

similar investigations on isolated hearts. He employed a modified method however in which the animal or human hearts were immersed in a water bath, and then irradiated with ultrasound. These experiments confirmed our findings that it was feasable to obtain echo signals from the heart walls.

Figs. 28—29 are from another experiment in which a thrombus removed during a commissurotomy operation and kindly put at our disposal by O Dahlbäck, the thoracic surgical specialist, was inserted into the cavity of the left ventricle in an isolated heart. The multiple echo signals obtained are probably due to the multi-layered consistency of the thrombus. When heparinised blood was used instead of water similar results were again obtained.

Blood vessels have also been examined in a similar way (31) Fig. 30 shows a picture from such an experiment, in which the pulmonary artery from a freshly slaughtered calf is placed in water and ultrasound is directed through it at right angles to its walls. It is apparent from the illustration that sound is reflected from both the external and internal surfaces of the vessel. Once again the same results were obtained by substituting heparinised blood for the water

SUMMARY

Investigations in 1953 and 1954 by Hertz and Edler using isolated heart preparations demonstrated that ultrasound can be used for the following

1. Localization of the interfaces between the heart walls and the enclosed blood-filled cavities.
2. Measuring the thickness of the heart walls.

INTRODUCTION

In 1954 Edler & Hertz (1) described how ultrasound could be used to produce continuous recordings of the movements of the heart walls. It was found that an echo signal of characteristic pattern was obtained when the ultrasound-generating crystal was applied to the third left interspace 1 to 4 cm lateral to the sternal margin. This echo signal represents some structure in the heart s interior lying at a depth of 6 to 8 cm from the chest wall, and some 2 to 4 cm anterior to the rearmost echo from the heart. The echo signal moves rapidly and the curve it describes can be correlated to the pressure variations in the left atrium (Fig 1) In earlier papers by Edler & Hertz 1954 (1) Edler & Gustafson 1957 (2) and Effert et al. 1957 (3) this echo was supposed to arise from the anterior surface of the left atrium. In mitral stenosis characteristic tracings are obtained. The method has been mainly used for estimating the degree of mitral stenosis, however during the course of these investi

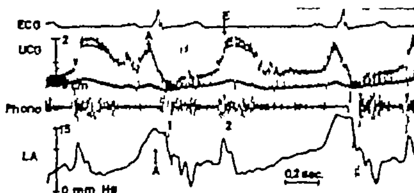


Fig 1. Ultrasoundcardiogram (UCG) recorded by direct writing electrocardiograph simultaneously with electrocardiogram, phonocardiogram and left atrial pressure (LA) The crystal was placed over the third left intercostal space. Wave A in the UCG corresponds to atrial systole. In the phonocardiogram 1 and 2 are the first and second heart sounds, respectively Clinical diagnosis Aortic insufficiency

Chapter VII

ECHOGRAMS FROM HEART STRUCTURES IN LIVING MAN THE ULTRASOUNDCARDIOGRAM

By applying the sound generating crystal to the chest wall in the precordial area, so that the sound beam is directed towards the heart, a picture is produced on the oscilloscope screen as shown in Fig 31. This was demonstrated by Hertz and the author 1954 (34) Soon after the emission signal 0, comes a powerful signal-complex R, consisting of one, or a number of strong confluent echo signals, which arise from the chest wall and any lung tissue overlying the heart at that point. When the crystal is placed over a rib, the amplitude of the echo



Fig 31. Echogram obtained with the crystal applied to the precordium. 0 = emission signal. R = echo signals from chest wall.

signals increases compared with those obtained over an interspace, this being explained by the high acoustic impedance of bone (6.1×10^3 gr/sq cm sec, see table 1, page 11)

When the beam is aimed suitably another echo signal (or signals) E appears on the screen further away from the emission signal 0. This signal, unlike R, moves back and forth along the x-axis. This is shown in Fig 32, which demonstrates filming of the echo signals on the screen. The sequence of photographs is taken at 24 frames per second. The correlation between the movements of the echo signals and heart's activity recorded by ECG, is apparent from Fig 33, which shows continuous recording as described on page 38, chapter V These pulsating echo signals are obtained only when the crystal is applied to the precordium and the beam directed towards the heart. Fig 34 shows recordings from different parts of the precordium in a normal individual. The echo signals pattern of movement varies according to the location of the crystal and the direction of the beam. If the

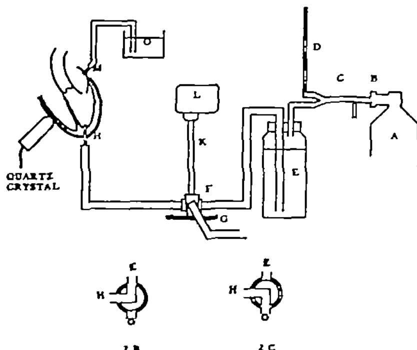


Fig. 2. A schematised picture of the experimental lay-out for producing valve movements. Figs. 2 B and 2 C show the positions of the tap for the production of high and low pressures in the tube leading t the left ventricle.

on the oscillograph screen. The timing was also indicated for each camera ex posure in the filming of the respective valve ostia.

Pressure fluctations in the left ven tricle were produced in the following manner The necessary pressure was provided by an oxygen cylinder (A) This was connected via a reducing valve (B) to a connector (C) which was partially open to the air By this arrangement a constant pressure could be maintained in the rest of the system. The connector (C) was in its turn at tached to a Y piece and the latter was connected to a mercury manometer (D) and a water filled pressure bottle (E) This communicated via a widbore tube with the three-way tap (F) This latter (F) was connected by tubing to the cannula (H) in the left ventricle, and by the tube (G) to a suction venturi with which reduced pressure was obtained. The tubing had an internal diameter of 12 mm. The tap (F) had two through-channels at right angles to each other An electric motor (L) with an output of 40 watts rotated the tap in an anticlock wise direction via the shaft (K) When the tap is in the position shown in Fig. 2 B the pressure bottle (E) is in connection with cannula (H) whereupon the pressure rises in the left ventricle After 90 counterclockwise rotation of the tap, Fig. 2 C, the pressure in the tube leading to the left ventricle dropped to a lower level. After a further 270 degrees of rotation the high pressure was restored. Thus was obtained a short quick pressure rise in the left

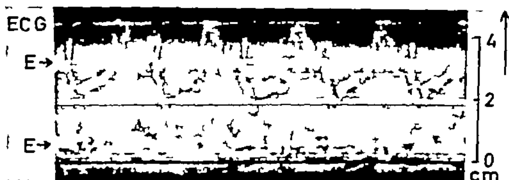


Fig 33 Continuous recording of the movements of the echo signal seen in Fig 32. Correlation between the movements of the upper echo signal E and the ECG is pparent from the picture

crystal is applied to the chest wall beyond the precordium, only the powerful, confluent, non-pulsating signal-complex R is normally obtained, and this is seen in the 3—5 cm zone adjacent to the emission signal 0 No pulsating echo signals can be obtained over the chest wall anywhere beyond the precordium. By applying the crystal to the jugular notch and directing the beam towards the aortic arch, however as Gustafson 1956 (61) pointed out, one can obtain pulsating echo signals on the screen at a distance from 0 proportional to the distance between the crystal and the aortic arch.

The powerful echo signals obtained over the 'non-precordial' parts of the chest wall arise not only from the latter but also from the underlying lung, since the air filled alveoli constitute a plentiful source of sound-reflecting interfaces. The reflexion index is high here, because of the big difference in acoustic impedance between human tissue (see table 1 page 11) and air (the acoustic impedance is 42.8 for dry air at 0 C and 760 mm Hg) Furthermore lung tissue absorbs sound to a high degree. According to Dussik (30) at a frequency of 1 Mc/s. the attenuation constant for pulmonary tissue is 30 decibels per centimetre of sound path, or $\alpha = 3.45$ per cm, while the value for bone is from 8 to 62 decibels [Güttner et al. 1952 (63)] It is the air content which causes this extensive absorption. Atelectatic lung has a considerably lower absorption constant.

If the heart is enlarged, pulsating echo signals can be obtained over a significantly larger area of the chest wall.

Displacement of the heart to either side implies a corresponding displacement of the 'recording area' on the chest wall. In patients with advanced emphysema together with median position of the heart, it can sometimes be impossible to record the pulsating echo signals because of interference from the intervening lung tissue. The same difficulty may also arise in obese barrel chested individuals.

The distance between the emission signal 0 and the rearmost echo signal has been measured with the crystal



Fig 3. A cross section of a calf' heart after completion of the experiment.

obtained with the ultrasound method, the distances in the latter case being 6 to 7 and 5 to 6 cm, respectively depending on the phase of movement. Hence those structures giving rise to the aforementioned echo signals lie at depths corresponding to the anterior mitral valve cusp and the posterior aortic valve cusps.

THE MOVEMENTS OF THE MITRAL VALVE

Fig 4 shows recordings taken on Mingograph paper At the top is seen the record of each film exposure produced by repeated interruptions of an alternating current disturbance. Beneath this is the pressure tracing from the left ventricle with below it the zero line. At the bottom is the ultrasound curve produced when the beam is directed as for needle A, Fig. 3. To facilitate understanding of the ultrasound curve s features the crystal can be imagined as being situated at the upper margin of the picture. As the echo giving structure approaches the crystal the tracing rises, and vice versa. Thus at the lowest point on the curve the reflecting structure is at its maximum distance from the crystal, and at its highest



Fig. 35. Echo signal recorded from the posterior wall of the heart in a normal case.

applied close to the midline in the fourth left interspace (34) The beam in each case was directed straight backwards at right angles to the anterior chest wall. The relationship between the distance thus measured corresponds to the distance, anterior chest wall — posterior heart wall as measured radiologically. In the normal heart this distance is 9—11 cm, but if there is marked enlargement the distance may be as much as 15 or 16 cm. This posterior wall echo signal moves about 1 cm towards the anterior chest wall during ventricular systole and recedes slowly again during diastole, Fig. 35. In aortic incompetence with dilatation of the left ventricle this posterior-wall echo signal has an increased range of mobility during systole (in such cases it can also be recorded in the fifth left interspace, often as far out as the mid clavicular line) and also exhibits a quick movement dorsalwards early in diastole Fig. 36.

When the crystal is applied over the third left interspace 1—4 cm from the sternal margin an echo signal is obtain-

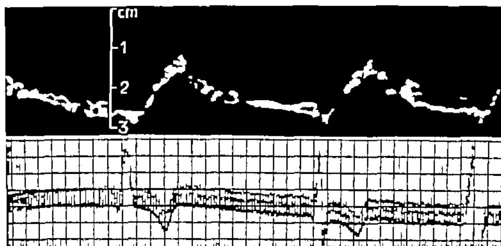


Fig. 36. Echo signal recorded from the posterior heart wall in a case of aortic incompetence with advanced enlargement of the heart.

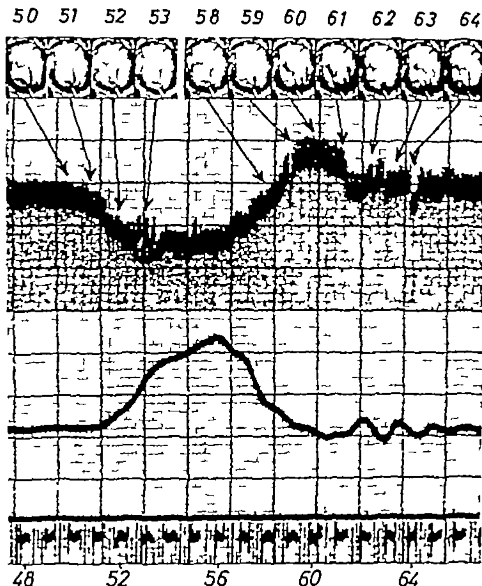


Fig. 5. Cycle 3 (Fig. 4) in close-up. Observe that the UCG curve has been shifted upwards to correlate it with the pictures of the mitral valve. The markings indicating film exposures have been moved downwards

point to the crystal. In pictures 62 to 64 one sees that mitral valve shows small fluctuations in its degree of closedness. Simultaneously small fluctuations in both pressure and ultrasound curve are recorded.

During the experiment the anterior mitral valve cusp was immobilised with a pair of forceps whereupon the echo signal became stationary and the ultrasound curve became flat. This signified that the echo giving structure

in the medial part of the fourth left interspace lies at a depth corresponding to the posterior wall of the left ventricle. This together with the appearance of its tracing, points to the posterior wall of the left ventricle as being the source of the echo [Edler & Hertz, 1954 (34)]

The multiple, confluent signals 1.5—2 cm beyond the foregoing arise from structures behind the heart (lung tissue and posterior mediastinum) The fact that the posterior heart wall signal lies about 2 cm in front of the lung tissue echoes, signifies that the former arises from the internal surface of the ventricular wall.

Further research is needed to discover the exact origin of the rapidly and widely oscillating echo signal, recordable in the third left interspace.

SUMMARY

1 With the ultrasound method described, echo signals can be obtained from various parts of the human heart in vivo.
2. The movement of heart structures can be continuously recorded, the resultant tracing being referred to as an ultrasoundcardiogram or UCG
3. By applying the crystal to the fourth left interspace a tracing can be obtained which represents the motion sequence of the left ventricle's posterior wall.

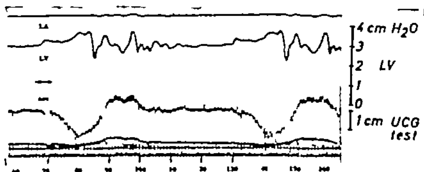


Fig 8. Simultaneous recordings of left atrial pressures, left ventricular pressures, the ultrasound curve (beam direction as in Fig 3 A) and the film exposures (51 per sec.)

is shown in Fig 10 The anterior mitral cusp is seen in the upper right sector of the picture. The frames are numbered 67 to 106. As is apparent, from 67 the ostium is open, slowly to close later In frame 76 and from frame 80—86 there are only insignificant degrees of valve opening, while from 77 to 79 closure is complete. Between 76 and 86 the echo emitting structure is at its furthest point from the crystal. From frame 87 onwards it opens, to reach its

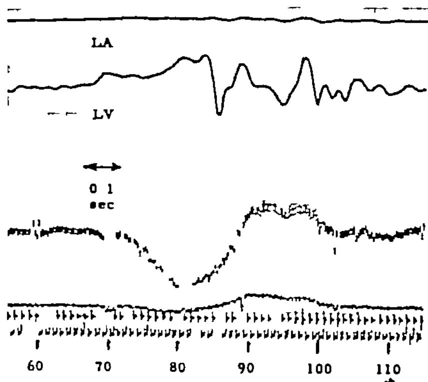


Fig 9 Cycl 1. (Fig 8) in close-up.

PART TWO

MITRAL AND AORTIC VALVE MOVEMENTS RECORDED BY AN ULTRA-SONIC ECHO METHOD — AN EXPERIMENTAL STUDY

BY
INGE EDLER, ARNE GUSTAFSON TORD KARLEFORS AND BO CHRISTENSSON

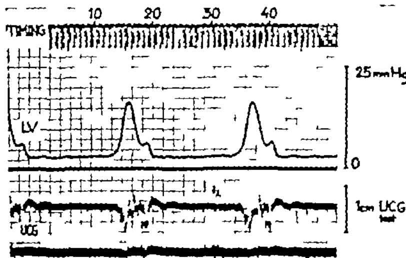


Fig 11. Simultaneous display of film exposures (18 per sec.) left ventricular pressure tracing and the ultrasound curve (beam direction B as in Fig 3)

fully open state) by frame 92. It is interesting to note that the ultrasound tracing at frame 76 coincides with that at frame 88. The ostium subsequently remains open until picture 100 and then begins successively to close again.

One is therefore justified in assuming that the anterior mitral valve cusp is the echo giving structure

THE MOVEMENTS OF THE AORTIC VALVE.

The aortic valve was studied using the same principle as that just described. In Fig 11 is shown, from above downwards, the markings indicating camera exposures and the pressure curve from the left ventricle with base line The ultrasound curve was obtained for the beam direction represented by needle B in Fig. 3. It is apparent that with the quick rise in ventricular pressure the echo giving structure recedes from the crystal, and approaches it when the pressure drops. This is repeated from cycle to cycle. Fixation of the left posterior cusp abolishes these movements. Details can be appreciated better in Fig 12, which shows the second cycle At the top is the film record of the appearance of the ostium. The left posterior cusp is at the extreme right of the picture. The camera was run at 18 frames per second. Individual exposures are numbered as before Below follow the ultrasound and pressure curves and the zero line, together with markings for film exposures. In picture 35 the ostium is closed. In picture 36 it is beginning to balloon simultaneously with the rapid pressure rise. Observe that here the ultrasound curve shows that the echo emitting structure begins to move before the ostium can definitely be seen opening At the open position in picture 37 this structure is furthest away from the crystal

) Because of the low pressures employed in these experiments complet valve opening was never attained

gations it has been found possible to demonstrate the presence of thrombi in the left atrium in two instances an atrial myxoma was revealed, (4, 5) and in several cases pericardial effusions were discovered (6)

In order to elucidate the exact origin of the aforementioned characteristic echo signal Edler & Christensson have carried out studies on cadavers. A needle was introduced through the chest wall in a position and direction corresponding to that previously taken by the ultrasound beam. The needle was found to have pierced the anterior wall of the right ventricle and to have passed on through the right ventricular outflow tract, the interventricular septum, the upper part of the left ventricle and, as a rule, via the mitral valve into the left atrium and out through its posterior wall. Among those structures through which the needle passes it is the anterior cusp of the mitral valve which having regard to its localization and movement pattern, could be responsible for the tracing produced by the echo signal in question.

The object of the present investigation has been to ascertain whether in fact the heart's valve cusps do reflect ultrasound. Since it was intended to produce easily controllable valve movements rather than to mimic the naturally occuring cycle of events, a method was chosen involving the use of hearts removed from calves or cows. Valve movements were then induced in these by causing pressure variations in the perfusing fluid.

Among earlier studies in which valve movements were induced in a similar way should be mentioned those of McMillan et al. 1954 (7) and Davila et al. 1956 (8)

For details of the technicalities of recording by the ultrasound method, reference should be made to the earlier work of Edler & Hertz (1) Effert, Hertz & Böhme (9) and Edler (10)

TECHNIQUE

The preparations have consisted of calf and cow hearts weighing between 1000 and 2000 gram, the pericardium being entirely discarded. The heart was mounted in the upright position on a stand. Fig. 2 is a schematised picture of the experimental set-up. All except one of the pulmonary veins were tied off. Into the patent one was fitted a plastic cannula (M) of internal diameter 5.5 mm. A plastic cannula (H) of internal diameter 9 mm was driven through the apex of the left ventricle into the interior of the chamber

To bring about movements of the valves and likewise to record them, an experimental apparatus was devised consisting principally of three parts, the first being a unit by means of which pressure variations were produced in the left ventricle, the second consisting of an ultrasound-generating crystal and a cathode ray oscillograph, and the third consisting of a pressure receptor (Svema, type EMT 456, Nr 11596) with electromanometer and a direct writing four channel Elema Mingograph. Paper speed was 50 or 100 mm per second. Pressures in the left atrium and ventricle were recorded together with the ultrasound echo's movements as seen

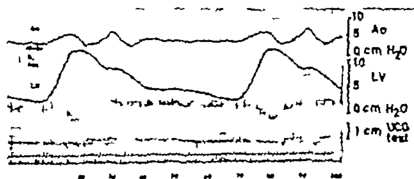


Fig. 13. Simultaneous recordings of aortic and left ventricular pressure changes, the ultrasound curve (beam direction B as in Fig. 3) and film exposures (51 per sec.)

immediately before the pressure has reached its highest value. Closure is beginning in frame 36. The pressure tracing clearly shows a catachrotic notch which is immediately followed by a movement in the ultrasound curve. These indications show that the structure moves firstly away from and then towards the crystal. In pictures 41 and 42 the echo emitting structure has reached its nearest point to the crystal. As previously the small oscillations in the

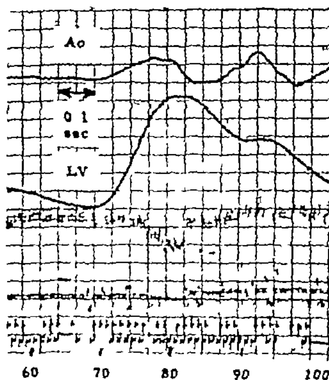


Fig. 14. Cycl. 2 from Fig. 13 in close-up.

ventricle followed by a longer period of reduced pressure The tap was rotated at a rate of 40 revolutions per minute. With the object of inducing a flow through the mitral ostium during the period of low pressure in the left ventricle, a cannula (M) in the left atrium was connected to a siphon arrangement (O) When pressure was high in the left ventricle water flowed from this chamber into the aorta. The whole system from the pressure bottle onwards was fluid filled. The right side of the heart was also filled so that air should not interfere with ultrasound recording Utilizing the experience gained in the previously described needle puncture experiments, recordings were done with the crystal placed against the anterior wall of the right ventricle at the junction of the upper and middle thirds.

Pressure recording was carried out in the left ventricle either by means of a catheter introduced via the left atrium and mitral ostium, or by a thick cannula driven through the ventricular wall and thereafter connected to a catheter this in turn being coupled to a pressure detector This latter was connected via an electromanometer to one of the channels of the Mingograph. Recordings of pressure variations in the left atrium were done in a similar way In order to permit later observation and filming of the action of the mitral valve cusps a portion of the auricular appendage was removed. The mitral ostium could thereby be inspected from above. There was then found to be a constant fluid level at 3 to 4 cm above the level of the valve. The aortic ostium could be similarly inspected through a window cut in the innominate artery immediately above its origin from the aortic arch.

Filming of the valve movements was done with a Paillard camera H 16 RX, f = 150 mm. This was set for speeds of 16 or 48 exposures per second. The actual speeds were 18 and 51 exposures per second.

RESULTS.

Echoes of characteristic movement pattern were constantly obtained with two different beam directions. The angle between these beam directions was about 15 degrees. Needle puncture experiments were then done to discover what structures would be encountered by beams travelling at such angles. Fig. 3 shows a preparation cut open after such an experiment. Needle A pierced the anterior wall of the right ventricle the interventricular septum, and passing through the upper part of the left ventricle transfixed the anterior cusp of the mitral valve, and left the heart via the posterior wall of the left atrium. Needle B passed through the anterior wall of the right ventricle, the interventricular septum, and the upper part of the left ventricular cavity just under the plane of the aortic valve cusps. The left posterior cusp (arrow) lies just above the needle.

Measured along the line of needle A the anterior mitral valve cusp lies 6.5 cm from the anterior wall of the right ventricle. The distance to the left posterior aortic valve cusp is 5.5 cm measured along the line of needle B. These figures agree closely with those predicted by the corresponding echoes

pressure tracing are reflected in small deviations in the ultrasound curve.

One can therefore safely say in view of the support offered by the needle-puncture experiments, that the echo giving structure in this instance is the left posterior cusp of the aortic valve.

As when the mitral valve was under investigation, the aortic cusp movements were photographed while small movements were induced by slight pressure changes, also at 51 frames per second. Fig. 13 shows, above the pressure curves from aorta and left ventricle respectively and below the ultrasound curve. In this experiment the echo represents the right posterior cusp of the aortic valve, as was demonstrated by immobilization of the cusp by the method previously described. The markings indicate film exposures. The second cycle can be examined in detail in Fig 14

In Fig. 15 is shown a sequence of photographs taken at 51 frames per second, these being numbered 60 to 99 The right posterior aortic cusp dominates the entire upper area of the picture The ostium is closed in pictures 60 to 75. It then begins to open and subsequently reaches maximal opening in frames 79 to 82, and successively closes thereafter In frame 88 no opening of the valve can be seen. Close examination of these pictures reveals that the situation prevailing in frames 60 to 74 does not recur until frames 97 to 99, showing that between 74 and 97 the valve has been in a different plane. The ultrasound tracing Fig 14 shows that the echo emitting structure begins to recede from the crystal at 74 and is at its furthest point at 79 to 81. The quick return movement immediately after 82 coincides with the beginning of the pressure fall in the left ventricle

This investigation demonstrates that with appropriate direction of the ultrasound beam the movements of the posterior aortic valve cusps can be recorded

SUMMARY

An experimental method for evoking movements in valve cusps in isolated heart preparations is described. The ultrasound method is demonstrated as being capable of registering movements of the mitral and aortic valves representing the anterior mitral cusp and the posterior aortic cusps, respectively

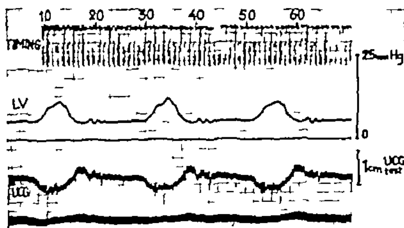


Fig. 4. Simultaneous recording of film exposures (18 per sec.) pressure variations in the left ventricle and the ultrasound curve (beam direction A as in Fig. 3)

point this structure is at minimum distance from the crystal. It follows from the figure that as the left ventricular pressure rises, so the echo giving structure recedes from the crystal. When the pressure falls the converse occurs. The pressure variations in the left ventricle are small. It is also clear that even tiny fluctuations are recorded by the ultra sound curve and faithfully reproduced cycle by cycle.

In Fig. 5, above, are pictures of the mitral valve ostium. The anterior cusp is to the right and the posterior lower down to the left. The pictures were taken at 18 frames per second with the camera pointing downwards and forwards. The number of each exposure can be seen above the pictures. From above downwards follow the ultrasound curve from the third cycle of Fig 4, the left ventricular pressure tracing, and marks indicating camera exposures. A scrutiny of the inter-relationships between the appearance of the ostium, the ultrasound curve and the pressure tracing at various definite times reveals the following. In pictures, 50 and 51 the ostium is very nearly closed — a little chink can be seen between the cusps. When the ventricular pressure begins to rise the cusps come together in pictures 52 and 53 and in these one also has the impression of the cusps ballooning towards the observer. This is brought out more markedly when the film is run through. The ultrasound tracing shows that the echo giving structure is furthest away from the crystal immediately prior to the left ventricular pressure reaching its highest value. When the pressure begins to fall the structure approaches the crystal again and picture 59 shows the ostium beginning to open. Maximal opening*) in pictures 60 and 61 when the pressure has reached its lowest level. The ultra sound curve now shows that the echo giving structure has reached its nearest

*) Because of the low pressures employed in these experiments complete valve opening was never attained.

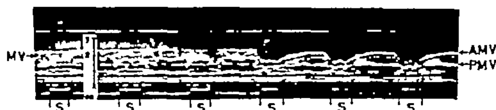


Fig 6. Immobilisation of the anterior cusp of the mitral valve with forceps. The ultra sound tracing is flat, (left) The characteristic curve returns as soon as the forceps are removed, (right) S = the rhythmically recuring periods of high pressure in the left ventricle. MV = the ultrasound tracing from the anterior cusp of the mitral valve.

became motionless with regard to the crystal. When the forceps were removed the typical ultrasound tracing reappeared, Fig. 6. If the cusp was moved towards the ventricular cavity by means of the forceps the echo signal approached the crystal, and vice versa.

Fig 7 shows the pressure tracing from the left ventricle and the simultaneously recorded ultrasound curve at the moment when intermittent perfusion was begun. During the first 2 or 3 'beats there were no or only slight pressure rises since the suction effect predominated. The associated pressure fall causes the echo signal to move towards the crystal, (the ultrasound tracing rises) and only after 4 or 5 'beats' do the previously described pressure rises and the characteristic ultra sound tracing appear

To elucidate in more detail the precise action of the valve cusps this process was filmed at higher speed, in this instance 51 frames per second. This time lower pressures were employed in the left ventricle in an attempt to see whether these were adequate to induce valve movements of an amplitude recordable by the ultrasound method.

As can be seen in Fig 8 a clear tracing was obtained confirming that valve movements can in fact be demonstrated by ultrasound even when the pressure differentials are small (shown by the relatively flat pressure tracing in the upper part of Fig 8) By enlarging the first cycle in Fig. 8 one can correlate the ultrasound curve and the pressure curve at every instant, Fig. 9 with the appearance of the valve ostium in Fig 10.

A portion of the film thus obtained

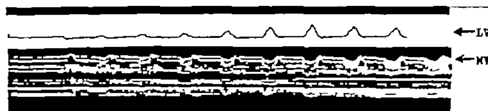


Fig 7 The pressure curve from the left ventricle (LV) and the ultrasound curve from th anterior cusp of the mitral valve (MV) recorded simultaneously t the start of an experiment.

mortem valvulotomy has also been studied in this way It was revealed that during systole the mitral valve cusps tend to bulge upwards toward the atrium and that the normal aortic valve opened to form a triangular orifice. This is in agreement with Leonardo s observations in 1513 (26, 21) Cinematographic studies of the action of atrioventricular valves performed in excised, surviving saline-perfused hearts of animals (25) also showed that during systole the cusps tend to bulge up towards the atrium. Rushmer et al. (23) studied the action of the mitral valves in intact dogs, using motion pictures of the images produced by x rays on fluorescent screens. This investigation revealed that the cusp-edges moved only very small distances.

In living man the study of valve movements first became possible with the development of x ray technique In patients with aortic or mitral calcification, valve movements can be visualized by fluoroscopy or by fluorographic film. Moreover the development of cardio-angiography and thoracic aortography in recent years has made it possible to visualize the normal valve cusps (3, 1)

Yoshida et al. (29) have used the ultrasonic Doppler method to obtain information on the movements of the heart (see chapter II pages 19 and 20) With this method the movements of the atrioventricular and semilunar valves can be recorded. By simultaneous recordings of ECG and phonocardiogram the opening and closing phases of these valves can be timed.

I. RECORDING OF THE MOVEMENTS OF THE ANTERIOR MITRAL LEAFLET BY THE ULTRASOUND ECHO-METHOD THE CURVE AM.

The appearance of the ultrasound cardiogram varies according to the point of application of the crystal and the direction of the beam, as mentioned in Part I, chapter VII. Fig 1 shows tracings taken from various parts of the left second third and fourth interspaces, in a case of persistent ductus arteriosus. Tracings 5 8 and 10 from the third left interspace and tracing 6 from the fourth left interspace show the characteristic appearance (indicated by an arrow) representing a structure having a movement amplitude of about 2 cm, referred to in chapter VII pages 63 and

Fig 1. Ultrasoundcardiogram recorded from arious areas of the precordium in a case of persistent ductus art riosus. The arrows on the diagram indicate the situation of the crystal in each case Tracing 1 is taken from the medial part of the "nd left interspace. Tracings 3, 5, 8 and 10 are taken from the 3rd left interspace with the beam directed antero-posteriorly Tracings 2 and 4 are from the 3rd left interspace with the beam directed 10—15 medially Tracings 6 and 7 are from the 4th left interspace with antero-posterior beam direction. Tracings 5, 8, 10 and 6 show the characteristic motion sequence with large amplitude.

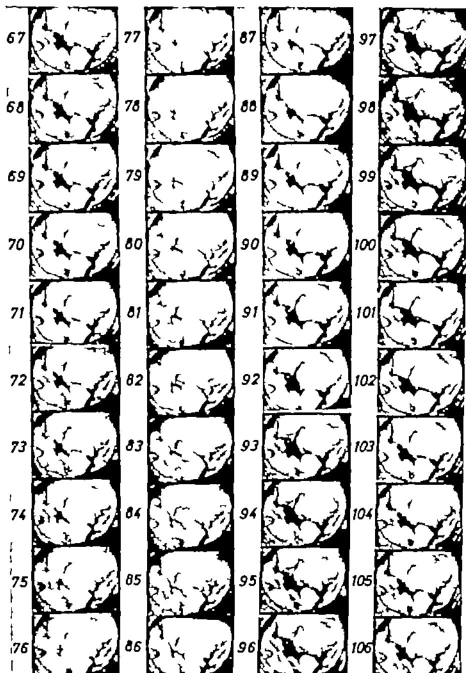


Fig. 10. The mitral ostium filmed at 51 frames per sec.

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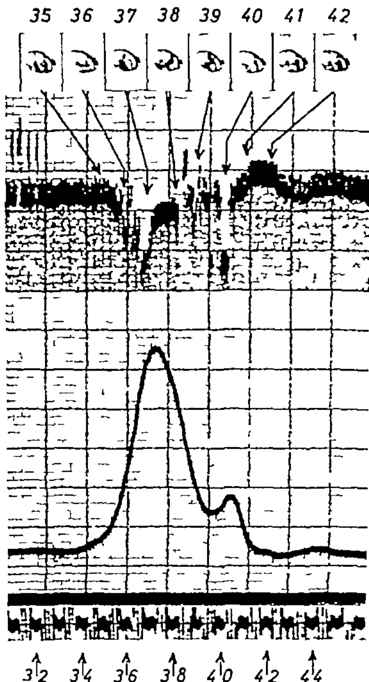


Fig 12. Cycle 2 (Fig 11) in close-up Note that the UCG curve has been moved upwards for correlation with the pictures of the aortic ostium. The exposure markings have been moved downwards

64 This type of tracing henceforth referred to as AM is easy to record since the echo signal, with its quick and typical motion, is easy to identify on the oscilloscope screen.

Earlier investigations of the tracing AM

When the tracing from the third left intercostal space in patients with mitral stenosis was first described by Hertz and the author (9) we presumed that it was derived from the anterior wall of the left atrium. Effert et al. 1957 (11) as well as Jacobi et al. 1958 (16) Gässler et al. 1958 (13) and Schmitt et al. 1960 (24) had come to the same conclusion. However no satisfactory proof for this assumption was given at that time.

In 1959 and 1960 however Edler et al. (8 a, 8 b, 9 a) have demonstrated the possibility of obtaining ultracardiographic records from the mitral tricuspid and aortic valve cusps in living subjects. The opinion was stated in these preliminary communications that tracing AM represented the action of the anterior mitral leaflet.

By making simultaneous recordings of the electrocardiogram and the ultra sound tracing AM the latter has been correlated to atrial activity (9 6, 15 7 8 10) The tracing AM has two peaks A and E, Figs. 2 and 3 representing the instants at which the echo-giving structure reaches its nearest point to the crystal on the anterior chest wall Normally A begins 0.08—0 12 sec after the start of the P-wave in the ECG (8) The same time relationship between the A wave in the UCG and the P-wave in the ECG is seen in atrioventricular block both partial and complete (6, 8 10) In atrial flutter the AM tracing displays multiple peaks corresponding in number to the flutter waves during ventricular diastole (6, 8, 10) In flutter or complete block, however A-waves have never been observed during ventricular

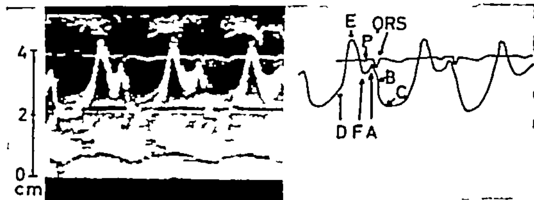


Fig 2. Left Tracing AM in a normal case Right Schematic representation of tracing AM in a normal case The rising curve represents the movement of the echo-source towards the crystal on the anterior chest-wall. The falling curve represents the movement of the echo-source away from the crystal. E represents the most ventral position attained by the echo-source and C — the most dorsal position The P wave in the ECG (V_1 and hence negative P) is followed by a peak A in the UCG record.

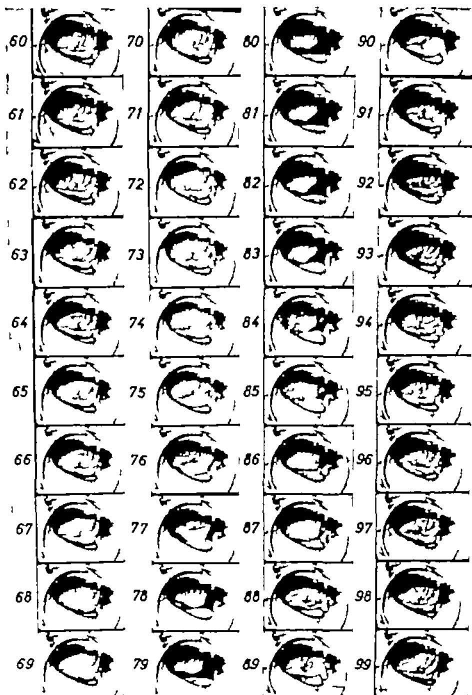


Fig 15. A rbo ostium filmed at 51 frames per second.

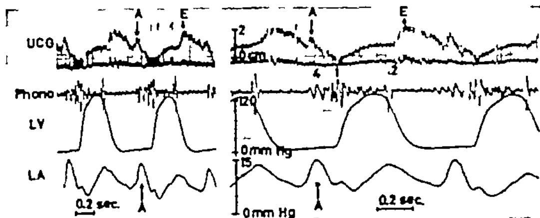


Fig 5 Simultaneous recordings of tracing AM, phonocardiogram, left ventricular pressure (LV) and left atrial pressure (LA) Direct writing method.
Left paper speed 50 mm per sec. Right paper speed 100 mm per sec.
The lowest point in the UCG curve is reached at th beginning of ventricular systole After 2nd heart sound, the UCG tracing rises steeply to peak F which is the highest point reached in the record. E is reached 0 10 sec after the 2nd heart sound.

flutter and atrial fibrillation, respectively

At the beginning of ventricular systole the tracing AM reaches its lowest point C, signifying that the echo-giving structure has reached its most distant point from the crystal on the anterior chest wall. After ventricular systole the tracing ascends steeply to the peak E, indicating the rapid forward movement of the echo-giving structure towards the crystal again. Effert (10) found that in normal cases the time interval between the second heart sound and the peak E is 0 11—0 16 sec with an average value of 0 13 sec. The total movement



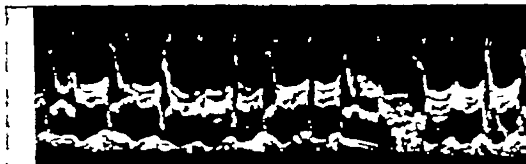
Fig 6 Complet atrioventricula block Two entricular complexes are seen in the ECG record (QRS is marked I and II) Each P wave is followed by peak A in the UCG record Th tim i t rval between P and A is 0 10—0 12 sec

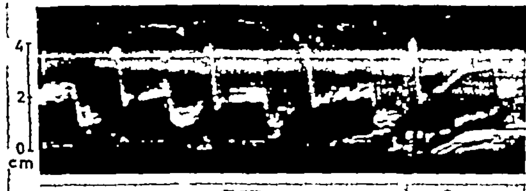
PART THREE

ATRIOVENTRICULAR VALVE MOTILITY IN THE LIVING HUMAN HEART RECORDED BY ULTRASOUND

BY

INGE EDLER




4
2
0
cm


4
2
0
cm



INTRODUCTION

The first description of the function of heart valves was, as far as is known, by Leonardo da Vinci. In Quaderni d'Anatomia published in the year 1513 he gave an account of his observations made during dissections of animal and human cadavers. Quaderni d Anatomia, which is preserved in the Royal Library at Windsor Castle, consists of a compilation of anatomical drawings and writings. Excellent reproductions of these original drawings with translations of the texts into English and German were published between the years 1911 and 1914 by the Norwegians Vangensten, Fonahn and Hopstock (26) More recently a further reproduction of Quaderni d'Anatomia was published by O'Malley and Saunders (21) Part II of Quaderni is concerned mainly with the *anatomy and physiology* of the heart, wherein Leonardo deals at length with the valvular apparatus. The atrioventricular and semilunar valves are depicted partly in the open and partly in the closed state. Leonardo concluded that the valves were capable of totally shutting an ostium, and further that the *deceleration of the blood-stream against* a closed valve results in the production of a sound. It is apparent from the drawings that Leonardo had observed the ballooned appearance of the atrioventricular valve-cusps when the valve is closed, and the triangular opening formed by the cusps of the semilunar valve when open.

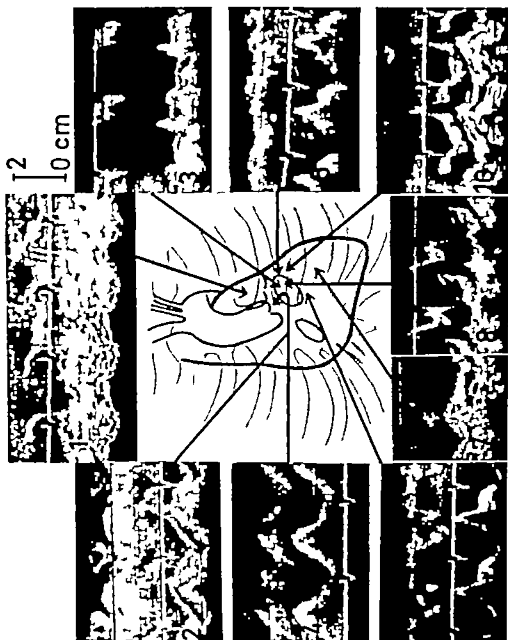
He demonstrated both mathematically and with sketches that a three-cusped valve is best suited to the aortic and pulmonary openings. A bicuspid aortic valve would offer greater resistance to the passage of blood, and a quadricuspid valve would be less effective in closing the ostium at high pressures.

During the last 150 years a considerable number of writers have carried out studies of valve function, using perfused hearts or excised heart valves together with artificial devices for producing pressure fluctuations (2, 12, 14, 5, 19 20) McMillan et al. (19 20) have used post mortem human hearts for cinematographic study of the movements in normal and stenotic aortic and mitral valves. The effect of post

Table 1

Measurements from tracing AM in 86 normal cases

Case no	Comment	Age	Chest depth (cm)	Heart rate per minute	Distance from emission signal O 1 point (cm) E interspace 3rd	E interspace 4th	C interspace 3rd	C interspace 4th	Distance (cm) E—F interspace 3rd	E—F interspace 4th	E—F (sec)
1		19	91	72	5.1	5.1	7.6	7 4	1.6	2.3	0.14
2		19	88	84	5.7	6 6	8 6	8.5	—	1.2	0 14
3		23	80	80	5 4	—	8.3	—	1.9	—	0.15
4		21	86	63	6.3	6 7	7.8	8.3	2.0	—	0 15
5		21	90	80	5.1	—	7.1	—	1.5	—	0 13
6		54	96	69	—	7.2	—	9.3	—	1.2	0 14
7		37	95	75	7.0	—	8 9	—	1 4	—	0.16
8		21	91	48	5.2	5 6	8.0	8 4	1.4	2.1	0 14
9		40	96	85	—	7.1	—	8.9	—	—	0.14
10		61	96	64	7.2	—	9.5	—	2.1	—	0.12
11		21	85	46	7.1	—	9.6	—	1.9	—	0.15
12		20	89	65	—	5.1	—	7.8	—	2.3	0.15
13		20	93	75	6.2	6 4	8 7	8.3	1.6	1.8	0.14
14		33	96	70	6.9	—	9 4	—	1.3	—	0.16
15		30	95	88	.2	7.1	9.5	9 4	1.5	1.3	0.12
16		40	91.5	60	6.0	6.6	8.2	8.8	1.5	1 4	0 14
17	Pulmonary emphysema ?	41	92.5	65	—	7 7	—	10 2	—	—	—
18		21	97	70	6 3	6.2	9.1	9 1	1.9	1.9	0 14
19		35	91	54	6 2	—	8 6	—	1.9	—	0 14
20		76	91	72	5 6	—	8 4	—	2 4	—	0 17
21		31	92	70	—	5 7	—	9.3	—	2 7	0 14
22		20	87	68	6 1	—	8 6	—	1.9	—	0 15
23		35	90	80	5.7	—	7 7	—	1.8	—	0 14
24		35	—	1?0	—	6 2	—	9 1	—	—	0 12
25		33	89	48	5.5	—	8 1	—	1 7		0 15
26		20	85	65	6 9	5 9	7 9	8.2	—	1 9	0 16
27	Pulmonary emphysema	63	90	—	—	—	—	—	—	—	
28		21	88	65	5.5	5.3	7.9	7.8	1.8	1.9	0 16
29		40	87	72	6.3	6 6	8 2	8 7	1.4	1 4	0 14
30		20	100	70	7 1	—	9.8	—	1 8	—	0 14
31		37	95	65	5.7	—	8.2	—	2 0	—	0 16
32	Recording in 5th interspace	36	86	88	6 9		9.5		2.1		0 14
33		32	89	65		6.8	—	9.2	—	1 7	0 16
34		20	84	75		6.3	—	8 7	—	1.8	0 17
35		20	81	90	4.0	4.5	7.5	7 5	2 6	1.5	0 15
36		44	95				—		—		
37		37	87	75	5.8	5 8	8 0	8.3	1.8	2 0	0 13
38		25	93	64	—	5 7	—	8 1	—	1.9	0 14
39		31	93	73	—	6 6	—	8.1		1.2	0 14
40		70	87	60	5 1	5 4	7 6	8 1	1 7	1 4	0 12
41		40	92	64		5 9		8.5	—	2.0	0 17
42		41	91	7?	6 6	6.5	7.9	8 4	—	1 9	0 12
43		49	93 5	55		6.5		9 1	–	0	0 18
44		20	86 5	76	6 1	5.0	7 4	7.5	1 4	1 4	0 15
45		31	97.5	75	6 4	6 0	8.	8 5	1 7	1.9	0 17
46		32	91.5	62	5 4	5 6	8.3	8 7	2 0	2.2	0 16
47		31	85	55	6 6			—	1.	—	0 14
48		8	94	62	5.8	5 7	8.2	8.2	1.2	1.8	0 15
49		39	101	85	6.3	6 5	8 4	9 0	1.5	1 7	0 16
50		1	86.5	60	5.2	5 5	7 1	7.8	1.5	1.3	0 14
51		33	94 5	55	6 4	6 7	8 7	8 9	1 1	1.3	0 13


2
0 cm

Interval 0—C, corresponding to the maximum distance between echo-source and crystal in each cycle was 82 mm from the third left interspace in 59 cases, with limits of 71 and 97 mm. The corresponding value for the fourth interspace was 83 mm, with variations between 71 and 102 mm.

Interval E—F measured from the third left interspace, was 17 mm, vary ing from 10 to 26 mm. The correspond ing values for the fourth left inter space were 17 10 and 27 mm.

Time-interval E—F varied from 0.12 to 0 18 sec with an average of 0 13 sec. The average speed for the movement E—F was 120 mm/sec. The mini mum speed for the movement E—F was 80 mm/sec.

Summary of findings.

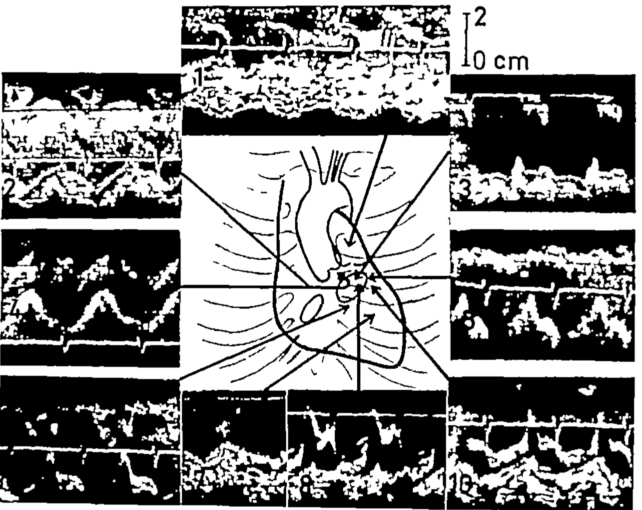
In a series of healthy men aged between 19 and 54 years the minimum echo-source — chest wall distance in each heart cycle as represented by tracing AM was found to be 58 mm, measured from the third left interspace The corresponding maximum distance in each cycle was 82 mm. The equiva lent values for the fourth left inter space were 59 and 83 mm, respectively Interval E—F was 17 mm recorded from the third as well as from the fourth left interspaces. Time-interval F—F never exceeded 0 18 sec

Conclusions.

For a valid interpretation of the ultra soundcardiogram, the heart must be considered in situ.

The heart structures which normally project onto the medial 3 4 cm of the third left interspace from which tracing AM is recorded are the following the anterior wall of the right ventricle the conus pulmonalis, the interventricular septum, the left ventricular outflow tract the mitral ostium and the left atrium. See Figs. 9 10 and 11 Of these it is the left atrium and the mitral valve which are affected by atrial activity Since in the adult the sagittal diameter of the heart is normally 85—90 mm (22) and the echo-giving structure moves along the sagittal line through the heart at a distance of 58—82 mm from the anterior chest wall it (the echo-giving structure) must be situated, at least during part of the cardiac cycle reasonably centrally in the heart. Thus the posterior wall of the atrium is excluded as a possible source of this echo. With regard to movement pattern and locali zation, therefore the echo-giving struc ture must be assigned to the anterior region of the atrium, in the vicinity of the mitral ostium. This localization accords with Virchow's findings (27 28) that in two powerfully built male cadavers, the middle of the aortic ostium was situated 55 mm and the middle of the mitral ostium 85 mm behind the sternum, respectively

From angiographic studies on patients in the supine position (3) it is known that the aortic ostium and valve cusps project onto the anterior thoracic wall at the left part of the sternum, or just lateral to the sternum at the level of the third left interspace and the sternal end of the fourth costal cartilage, or even at the fourth left interspace. Further more the mitral ring projects onto the third left interspace and fourth costal


2
0 cm
1
2
3

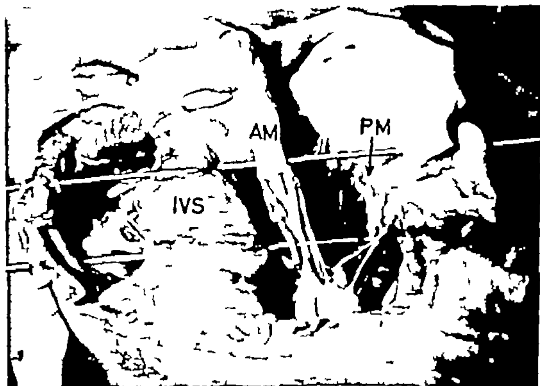


Fig 10. Same preparation as in Fig 9 but the lateral or left part of the mitral funnel has been cut away IVS = interventricular septum. AM = anterior mitral leaflet. PM = posterior mitral leaflet.

leaflet of the mitral valve thus hangs like a curtain in the central part of the left ventricle suspended from the anterior region of the root of the aorta. (17) See Fig 10 The anterior mitral leaflet constitutes the dorsal limit of the left ventricular outflow tract, and its surface projection is onto the sternal end of the third left interspace the fourth left costal cartilage and usually even the fourth left interspace

The mitral leaflet can be visualized in lateral views during angiocardiography (3, 1) The anterior leaflet occupies the frontal plan t king a caudal direction from the posterior limit of the aorta. Thus it could well present an angle of 90 to an impingeing sound beam directed from the anterior chest wall.

The anterior wall of the left atrium is proximal and to the right of the mitral osthum. Its projection onto the chest wall, therefore occupies only that part of the third left interspace which immediately borders the sternum. Normally the anterior wall of the left atrium does not reach so far caudally as to project onto the fourth left interspace where tracing AM can often, in fact, be recorded.

The anterior limit of the left auricular appendage projects onto the third l ft costal cartilage and sometimes onto the third left interspace It is consequently

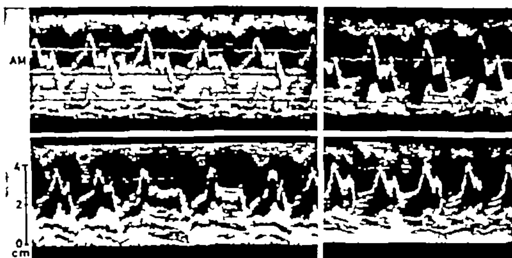


Fig 3. Tracing AM in four different normal cases, all with different heart rates. Below and to the left — sinus arrhythmia. Below and to the right — rising heart-rate. When this reaches a maximum, peak A disappears

systole. In atrial fibrillation, A waves are absent from the UCG-tracing. A waves are thus connected with atrial systole. Figs. 4 and 5 show simultaneous recordings of the UCG phonogram and intracardiac pressure changes. Figs. 6, 7 and 8 show curve AM in cases of complete atrioventricular block, atrial

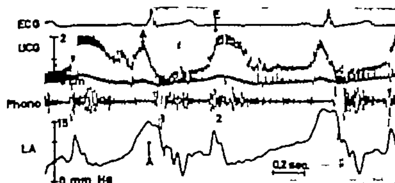


Fig 4 Simultaneous recording of ECG, tracing AM, phonocardiogram and left trial pressure LA (recorded by suprasternal puncture ad modum Radner) in a case of aorti incompetence. Direct writing method. In the phonocardiogram figures 1 and 2 indicate the first and second heart-sounds. Atrial systole, indicated by the letter A in the pressure curve, is synchronous with peak A in the UCG E in the UCG represents the tim when the echo-source is closest to the crystal. From the figure it is apparent that tracing AM rises with increasing pressure in the left atrium and falls with diminishing pressure in the left atrium. The echo-source thus approaches the crystal on the anterior chest-wall with rising atrial pressure, and recedes from the crystal with falling pressure.

in the age group 19 to 54 years the characteristic ultrasound record was obtained from the medial end of the third and/or the fourth left inter spaces.

2. In 60 cases the record AM was obtained with the crystal placed over an area of the third left interspace between 2.5 and 4 cm from the mid line In 5ı cases tracing AM was also obtained from the fourth left inter space in the area from 2.5—4 cm from the sternal midline In 19 cases this tracing could be obtained only from the fourth left interspace

3. The echo-source approached nearest to the crystal on the anterior chest wall early in ventricular diastole In 77 normal cases the closest point reached was 40—77 mm from the chest-wall, the average distance being 58 mm.

4. The echo-giving structure receeded maximally from the chest-wall at the beginning of ventricular systole The maximum crystal—echo-source distance in 77 normal cases was 1—10" mm with a mean value of 82 mm.

5. The behaviour of the echo-source can be correlated with atrial activity The former moves in a ventral direction during atrial systole During ventricular systole the echo-source is at its most remote position relative to the crystal on the chest wall

6. The localisation of the echo-source within the heart and its behaviour pattern during the various phases of the cardiac cycle indicate that the structure responsible is the anterior leaflet of the mitral valve

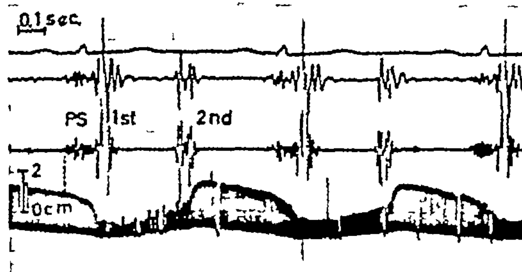


Fig 12 Tracing AM in case of mitral stenosis Simultaneous recording of ECG, phonocardiogram and I (T) by direct writing method PS presystolic murmur 1st and 2nd heart sounds ar labelled accordingly After the 2nd heart sound, tracing AM rises steeply Aft highest point is reached it falls again lowly Later at the time of [illegible] PS the tracing fall mor steeply

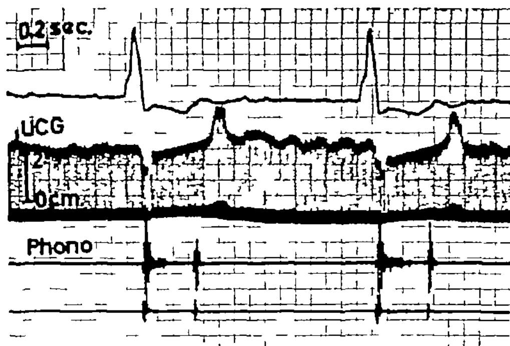


Fig 7 Atrial flutter alternating with trial fibrillation in a case of corrected trans position. Complete atrioventricular block. Simultaneous recordings of ECG, UCG and phonocardiogram. During ventricular diastole can be seen multiple waves representing atrial activity The waves vary in amplitude. During ventricular systole the multiple waves are absent in UCG

amplitude (the distance between the lowest point C and the highest point E on the tracing) according to Effert represents 19 to 30 mm with an average of 24 mm.

Normally the tracing falls rapidly from the peak E to point F see Figs. 2 and 3. In both normal patients and in those with congenital heart disease or aortic valve defects without simultaneous mitral defects, Edler and Gustafson (8) found that this movement takes place at a speed corresponding to 85—150 mm/sec. Effert (10) quotes 86—200 mm/sec with an average value of 125 mm/sec.

Summary

In earlier investigations it has been shown that for tracing AM, the following holds true

1 The distance from the crystal to the echo-source is greatest during ventricular systole, synchronously with the systolic pressure-drop in the atrial tracing. The echo-source reaches its nearest point to the crystal at an instant coinciding with early ventricular diastole.

2. The echo-giving structure has a clear relationship to atrial activity and it moves in a ventral direction during atrial systole.

3. Normally the interval between the

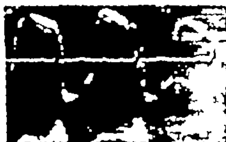








Fig 14 Tracing AM in a case of mitral stenosis.
Above left tracing taken on 21 3 1955 before commissurotomy
Above right tracing taken on 19 4 1955 after commissurotomy
Below left tracing taken on 22. 7 1959 before re-operation
Below right tracing taken on 1.10 1959 after re-operation.
At the first operation carried out by professor P Sandblom on 31 3 1955 the mitral ostium dmitted the tip of the little finger prior to commissurotomy After commissurotomy the entire index finger could be inserted quite easily
At re-operation carried out by Dr O Dahlbäck on 21 9 1959 the mitral ostium failed to admit the tip of th little finger Dilatation was performed with Oswald — Tubbs dilator the instrument being opened t 35 mm

were obtained in those cases having a stenotic element.

Method for measuring the rate of movement of the anterior mitral leaflet during ventricula dia tole in mitral st on s

As a measure of th rat of dorsal ward movem nt of the ant rior mitral cusp during entricular diastol Edler and Hertz (7 15) used the angle formed by the horizontal and tracing AM during its fall from peak F (horizontal line = time axis) See Figs 13 and 15

Sources of error

Since the degree of mitral stenosis is determined by measuring the angle a in the UCG it is necessary to investigate

second heart sound and peak E in the UCG is 0.11—0.16 sec.

4. The movement E—F normally takes place at a speed of 85 mm/sec or more.

Present investigation of tracing AM in a series of normal patients. The localization of the echo-source within the heart.

In order to determine the localization of the heart-structure from which tracing AM emanated, the author has carried out an investigation in a series of normal subjects.

Method

On the tracings, the distance has been measured between the line representing the emission signal 0 and points A, C, E and F. Since the aim of measurements is to achieve only approximate localization of the structure concerned, each of the points represents in fact the average value derived from three successive cardiac cycles. This is justifiable because of the small degree of variation at each point (max. 4 mm).

Fig. 8 a. Tracing AM in atrial fibrillation. The A-waves are absent.

Above: Rapid ventricular rate. In ECG record (reproduction poor) QRS complexes are indicated by figures 1—11. Between QRS complexes 3 and 4 the time interval is only 0.3 sec, and peak E is absent. The same applies between 9 and 10.

Below: Slow ventricular rate.

Fig. 8 b. Tracing AM in atrial fibrillation. A-waves are absent.

Above: A case with otherwise no signs of heart disease.

Below: A case of mitral stenosis.

Recording of tracing AM in normal cases. Case selection.

The series consisted of 86 healthy serving members of the Air Force in the age group 19—54 years.

Recording

Tracings were recorded in the usual way with the patients in the supine position. The crystal was applied to various parts of the left third and fourth interspaces.

Results

With the beam directed antero-posteriorly from the third or fourth left interspace 2.5—4 cm from the midsternal line, the tracing AM was obtained in 77 out of 86 cases examined, fragmentary tracings in 2 cases and no tracing at all in 5 cases. In 38 cases the record AM was obtained from both the third and the fourth interspace. In 22 cases it could be recorded only from the third interspace, and in 19 cases only from the fourth. Table 1.

In 2 cases (no 32 and 79) the tracing AM was obtained in the fifth left interspace. These were 2 of the 7 cases in which tracing AM could not be obtained from the third and fourth left interspaces.

Interval 0—E representing the minimum distance between the crystal on the anterior chest-wall and the echo-source, in each cardiac cycle, was 58 mm from the third left interspace in 60 cases, the limits of variation being 40 and 72 mm. In 57 cases the corresponding value for the fourth left interspace was 59 mm, the limits of variation being 45 and 77 mm.

the relative error due to this source is 7 % at the most. It should be kept in mind, however that the size of this error decreases appreciably with increasing α.

3 The errors due to this cause are dif ficult to assess correctly but because of the high quality optical systems used (Objective 40 mm Xenon 1 1.9 with close-up attachment) it can be estimated that they will be less than 2 %

Summing up the different errors in determination of the x-coordinate it is found that a maximal error of 10 % might arise due to the above named causes. There might be however another much more serious cause of error which is due to the fact that the exact localiza tion of the place on the mitral valve where ultrasound is reflected is not known and might vary appreciably from case to case. The fact that this error is not so large as to make the determina tion of the degree of mitral stenosis by the angle α impossible can probably be explained by the circumstance that the ultrasound must impinge perpen dicularly upon the valve for the genera tion of an recordable echo signal, since only then does the reflected sound strike the crystal transducer This factor cer tainly narrows down the possible reflec tion zone appreciably

Since the error in v is due only to irregularities in the speed of the motor and the gear mechanism, it is primarily dependent on the stability of the AC-mains frequency which has been given to within 0.5 This naturally pre-supposes that there is no slip or irregu larities in the gear wheels. Since appre-ciable attention and experimental work has been given to this problem it is felt that the error due to this source is negligible Thus, the relative error $\Delta v/v$ will be less than 1 %

Finally the error in t has to be discussed. This error is due to finite width of the slot in front of the film, which is 0.3 mm. Since the length vt on the film, which is usually used for the measurement of α is about 5 mm, the relative error due to this cause might be about $0.3/5 = 0.06$ or 6 %

Using the above equation we thus find the maximum error in the photo-graphic method to be 17 % Since the estimations made above are somewhat uncertain it would however be advis-able to assume a maximum error of 20 % for small magnitudes of α.

The direct writing method

Since in the transit time—voltage conversion apparatus a multivibrator circuit is triggered by the echo signal to be recorded, the form, i. e amplitude and rise time of this signal is likewise of the same importance as in the photo-graphic method. As the circumstances in both methods are very similar we must here too assume an error of 7 % for the x-coordinate because of the amplitude variations of the echo signal during recording Further since two electronic time determinations of highly stable circuits are used for the transit time measurement of the ultrasound pulse we must double the error estimat ed above due to this source thus giving 2 % The total error in the x-coor dinate is thus 9 %

Case no	Comments	Age	Chest girth (cm)	Heart rate per minute	Distance from emission signal 0 to point (cm): E interspace 3rd	E interspace 4th	C interspace 3rd	C interspace 4th	Distance (cm) E—F interspace 3rd	E—F interspace 4th	E—F (sec)
52		33	92	70	6.3	—	8.7	—	1.7	—	0.16
53		31	92	75	—	5.7	—	8.0	—	2.1	0.15
54		20	85	74	4.8	—	7.5	—	1.2	—	0.12
55		20	84	76	5.3	5.9	8.1	8.1	1.7	1.6	0.13
56		39	97	78	6.1	6.4	8.6	8.7	1.7	1.5	0.15
57		35	87	62	6.2	—	7.8	—	1.0	—	0.12
58		21	78	88	5.5	5.3	7.5	7.7	1.4	2.4	0.13
59		36	92	74	5.9	6.1	8.2	8.3	1.6	1.6	0.16
60		21	87.5	60	5.4	5.4	7.7	8.4	1.4	2.1	0.16
61		21	87.5	44	4.8	5.4	7.7	7.8	2.0	1.4	0.16
62		21	96	65	5.2	5.5	7.8	6.6	2.1	2.7	0.14
63		22	86	95	—	5.4	—	8.3	—	1.2	0.13
64		23	91	80	5.1	5.0	7.3	7.8	1.4	2.0	0.16
65		54	87	—	—	—	—	—	—	—	—
66		37	96	63	5.7	6.6	8.0	8.7	1.2	1.6	0.16
67		21	85	62	—	4.8	—	7.1	—	1.9	0.14
68		41	96	72	6.6	6.7	8.4	8.5	1.2	1.2	0.14
69		30	85	70	5.2	6.3	7.6	7.8	1.6	1.6	0.16
70		46	96.5	68	6.4	—	8.8	—	1.9	—	0.16
71		25	90	70	5.7	—	7.8	—	1.5	—	0.16
72		33	93	64	6.0	6.4	8.3	8.7	—	2.0	0.14
73		40	87	66	5.5	5.4	7.4	7.1	1.3	—	0.16
74		26	95	60	—	6.6	—	7.9	—	1.6	0.16
75		24	83.5	62	5.3	5.4	7.8	7.6	1.4	1.6	0.17
76		33	91	65	5.8	—	8.9	—	2.4	—	0.16
77	Obesity	43	109	—	—	—	—	—	—	—	—
78		45	91.5	80	6.6	—	9.1	—	1.7	—	0.14
79	Pectus excavatum. Recording in 5th intersp.	47	93	80	6.7		9.7		2.3		0.14
80		20	82	80	7.1	—	9.7	—	1.4	—	0.17
81		32	84	62	4.3	4.8	7.5	8.1	2.1	2.0	0.16
82		40	89	—	—	—	—	—	—	—	—
83		37	96	70	—	6.6	—	9.0	—	2.0	0.14
84		20	83.5	80	5.0	5.1	7.9	7.4	1.9	1.0	0.12
85		21	83.5	62	—	5.2	—	7.5	—	1.5	0.13
86		20	84	60	—	5.6	—	8.3	—	2.1	0.16
	Mean	30.7	89.4	—	5.8	5.9	8.2	8.3	1.7	1.7	

Table 2.

Heart catheterization data and the speed of tracing AM during ventricular diastole in 50 cases of mitral stenosis.

Case no	Age	Diagnosis	Pressure (mm Hg) Pulm. artery	Pressure (mm Hg) Pulm. wedge	The fall of tracing AM during ventr diastole (mm/sec)	Angle α in degrees
1	47	MS	25/12	12	37.1	42
2	51	MS+MI	42/20	16	21.6	25
3	23	MS	32/15	20	16.2	22
4	42	MS	106/45	25	11.9	17
5	23	MS+AS	30/19	12	38.7	44
6	45	MS+AS+AI	49/21	30	31.4	38
7	49	MS+AI	49/29	31	6.8	10
8	29	MS	42/22	23	21.2	28
9	45	MS	34/17	20	10.8	15
10	48	MS	78/42	26	7 7	11
11	29	MS	25/12	14	20 7	27
12	47	MS+MI	72/35	29	9.2	13
13	46	MS+AI	45/23	30	26.1	33
14	29	MS	80/37	26	9 4	13
15	58	MS	32/13	12	15.5	21
16	40	MS	60/34	33	12.7	19
17	45	MS	54/26	25	12.4	18
18	47	MS	65/35	32	8.2	15
19	35	MS	47/25	25	9.9	14
20	47	MS	55/25	27	11 5	16
21	36	MS	23/10	10	10.6	15
22	40	MS	40/16	28	10.9	15
23	34	MS	36/17	22	20 6	27
24	48	MS	55/28	32	21.6	28
25	33	MS	37/18	21	15.3	21
26	44	MI+MS	55/25	30	30.4	37
27	26	MS	55/30	35	10 1	14
28	40	MS	50/20	25	20 7	27
29	26	MS	25/14	18	26 6	34
30	32	MS+MI	45/25	24	16.5	22
31	47	MS	40/20	22	13.0	18
32	41	MS+MI?	55/25	29	12.5	17
33	49	MS	43/20	23	6 9	10
34	41	MS	70/32	31	8 4	12
35	51	MS	85/45	33	7 7	11
36	47	MS+TS+AS	45/20	25	9.9	14
37	39	MS	90/40	30	11.6	16
38	43	MS+AI?	75/45	44	12 6	19
39	47	MS	45/20	22	12.4	17
40	55	MS	105/40	36	2.9	6
41	26	MS+AI	37/20	23	25 5	33
42	40	MS	50/25	23	11.5	16
43	52	MS	103/40	33	6 7	10
44	24	MS	50/25	31	16 9	23
45	30	MS+AI	38/18	22	20.3	30
46	43	MS	45/25	26	8.4	12
47	46	MS	55/25	22	10.6	15
48	45	MS	55/28	28	12.3	21
49	49	MS	125/55	28	5 7	8
50	44	MS+AS	55/30	28	16.3	25
Mean					20.1	

MS = mitral stenosis. MI = mitral insufficiency TS = tricuspid stenosis.
AS = aortic stenosis AI = aortic insufficiency

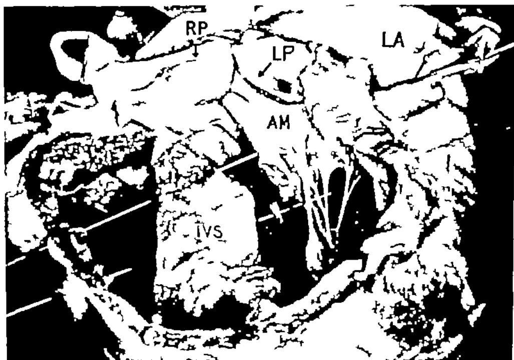


Fig 9 Section of a heart with left ventricular hypertrophy Picture taken from obliquely upwards. On left is right ventricular cavity on right is left ventricular cavity IVS = interventricular septum. AM = anterior mitral leaflet. LP = left posterior aortic cusp In the corresponding aortic sinus can be seen the opening of the left coronary artery RP = right posterior (non-coronary) aortic cusp. LA = left atrium.

Before the thoracic cavity had been opened, the needles which transect the preparation had been inserted in an antero-posterior direction from the 3rd left interspace (upper needle) and 4th left interspace (lower needle) at the sternal margin. Due to advanced hypertrophy and the continued presence of rigor mortis, the ventricular muscl was rigid and the heart retained its original shape during manipulation. Between the upper part of the interventricular septum and the anterior mitral cusp, can be seen the left ventricular outflow tract. The anterior mitral cusp in fact, constitutes the posterior limit of the left ventricular outflow tract.

With regard to the heart valves, the terminology used has been that based on the situation of the valves with reference to the main body-axis. According to this system the aorti valve consists of an anterior (coronary) cusp, a left posterior (coronary) cusp and a right posterior (non-coronary) cusp.

The preparation is from a series of transfixion studies by Edler Christensson and Gustafson. T be published.

cartilage between the sternal margin and approximately 2 cm lateral thereto. The anterior mitral cusp has a double fibrous attachment (17) It is fixed at its base, partly to the anterior part of the left atrioventricular annulus and partly to the posteriorly-directed segment of the aortic annulus. The anterior

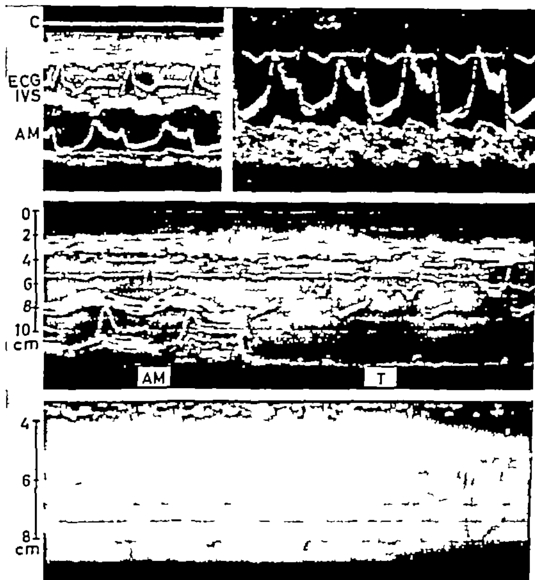


Fig 16. Tracings representing the action of the mitral and tricuspid valves in a case of trial septal defect. The crystal was applied to the 4th left interspace 5 cm from the midsternal line.

ABOVE antero-posterior beam direction.

Left Small-scale picture. AM represents the anterior cusp of the mitral valve. The minimum and maximum distances between AM and C (representing the crystal on the anterior chest-wall) are 8.0 and 10.2 cm, respectively IVS = interventricular septum.

Right Tracing AM to bigger scale (x-axis magnification)

MIDDLE Whil recording of tracing AM is in progress the direction of the beam is altered so as to diverge 15—20 medially from the antero-posterior line. Hereupon tracing AM disappears, to be replaced by tracing T representing the anterior leaflet of the tricuspid valve The minimum and maximum distances between T and C are 4.5 and 8 cm, respectively

BELOW Tracing T to greater scale



Fig 11. Same preparation as in Figs. 9 and 10 Depicted as seen from in front and somewhat above. IVS = interventricular septum. AM = anterior mitral leaflet. LP = left posterior aortic leaflet. RP = right posterior aortic leaflet. LA = left atrium

situated too far proximally to be responsible for the tracing in question.

The chordae tendinae belonging to the anterior mitral leaflet project onto the fourth left interspace and the fifth left costal cartilage and can therefore not give rise to echo signals recorded in the third left interspace.

The characteristic ultrasound tracing AM which is recorded from the third left interspace and/or the fourth left interspace consequently represents some structure, which, having regard to its localization within the heart and to the pattern of the movement recorded, corresponds to none other than the anterior mitral leaflet. The remainder of the left atrium does not comply either as regards area of propagation, or depth, from which the echo can be received.

As demonstrated by the author and co-workers in their experiments on the isolated heart (part II) it is possible with the crystal applied to the anterior wall of the right ventricle, to record an ultrasound tracing from the anterior cusp of the mitral valve.

Consequently the tracing AM represents the movements of the anterior leaflet of the mitral valve during the various phases of the cardiac cycle.

SUMMARY

1. In 77 out of 86 healthy individuals

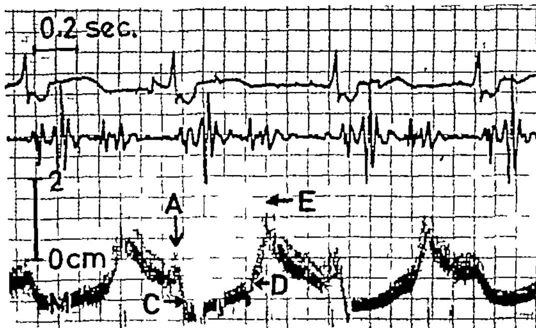


Fig 18. Action of anterior mitral leaflet recorded synchronously with ECG and apical phonogram in a case of atrial septal defect with right sided bundle-branch block (see Fig 17) The crystal was applied 5 cm from the mid-sternal line in the 4th left inter space, and the beam directed antero-posteriorly Paper-speed 50 mm/sec. There is wide splitting of the first and second heart sounds. Peak A corresponds to the systolic pressure-rise in the left atrium. Point C is synchronous with the first component of the split first sound.

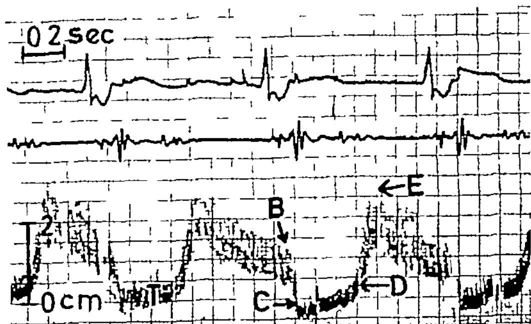


Fig 19 Action of anterior tricuspid leaflet recorded synchronously with ECG and apical phonogram Same case as in Fig 18. The ultrasound tracing is recorded with the crystal 2—3 cm from the mid-sternal line in the 4th left interspace. Beam direction 15—20 medially Paper speed 50 mm/sec. The first and second heart sounds are split. Peak A is absent or poorly recorded, wherefore the beginning of the quick phase towards C is here indicated by letter B. Point C is synchronous with the second component of the split first sound.

Recording of tracing AM in mitral stenosis.

In mitral stenosis the appearance of tracing AM is entirely different. Figs. 12 13 and 14. The quick component E—F is lacking and the tracing shows a slow fall, as a rule continuing as far as points A or B Peak A is usually absent in mitral stenosis. The characteristic appearance of the tracing in mitral stenosis has been pointed out previously by Edler and Hertz (7 15) and these findings have since been confirmed by others. The author has been able to obtain these typical records in 338 out of 346 cases of mitral stenosis. In only 8 cases of mitral stenosis was it impossible to record the typical tracing from the anterior mitral leaflet. In 2 cases the probable explanation lay in the patients' obesity In 5 cases emphysema was present, which in all probability rendered recording impossible In 1 case the likely factor was advanced displacement of the heart to the right, a sequel of rightsided lung changes. In 621 cases of mitral disease investigated by Effert (10) similar tracings





Fig 13 Tracing AM in a case of mitral stenosis. Recording by photographic method. Above, before commissurotomy Below after commissurotomy indicates the angle between the horizontal line and that portion of the tracing which represents AM movement during ventricular diastole. The smaller the movement of the echo-source the smaller becomes this angle.

of the split second sound this lag is the same, 0 08 sec. Immediately after the pulmonary component of the second sound, the echo-giving structure in the tricuspid valve makes a quick movement towards the anterior chest wall, for which reason it can be concluded that this structure is, in fact, the anterior cusp.

In normal cases only fragmentary tracings have hitherto been obtained from the tricuspid valve. In one of our cases having cor pulmonale with decompensation, such recordings of tri cuspid valve action were obtained. The same type of tracing has been described by Effert (10) in 3 cases of mitral stenosis with pulmonary hypertension and tricuspid incompetence. Effert con sidered, however that the tracing ema nated from the wall of the right atrium, analogous with the then current inter pretation of the mitral valve tracing.

SUMMARY

1. Ultrasound tracings from the tricuspid valve have been recorded in 10 patients with atrial septal defect.

The anterior cusp is shown to be responsible for these tracings.

2. By means of simultaneous UCG ECG and phonocardiogram recordings by the direct writing method it has been possible to demonstrate correlation between the action of the mitral and tricuspid valves and the heart sounds

the magnitude of possible errors in this measurement, since these may influence the reliability of the method. This angle is determined by the equation (cf Fig. 15)

$$tg\,\alpha = \frac{x}{vt}$$

when x is the movement of the mitral valve during time t, and v the velocity of the film or the ECG-paper in the recording apparatus. By differentiation we find

$$\frac{d\,(tg\,\alpha)}{d\,\alpha} = \frac{dx}{x} - \frac{dv}{v} - \frac{d}{t}$$

which shows, that the relative error in t α (and thus, approximately also in α providing that $\alpha < 60$) is equal to the sum of the relative errors in x, v and t.

Thus, since $\frac{d\,(tg\,\alpha)}{tg\,\alpha} > \frac{d\,\alpha}{\alpha}$ for values of α occuring in these measurements

$$\frac{d\,\alpha}{\alpha} \leq \frac{dx}{x} + \frac{dv}{v} + \frac{dt}{t}$$

gives the maximum relative error to be expected in α. In the following the possible errors will be discussed for the photographic and direct writing method separately

Photographic method.

In this case an error in x may arise from several causes, which may be put down as follows

1 Changes in the sweep-velocity of the electron beam.

2 Changes in the amplitude of the triangle-formed echo signal.

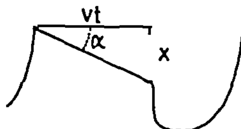


Fig 15 Schematization of tracing AM in mitral stenosis Angle is a measure of cusp-movement (x) during ventricular diastole. See text.

3. Changes because of distortion caused by the optical system in the camera as well as in the enlarger

These sources of error can be estimated as follows

1. Since the scale of the instrument (and thereby the sweep-velocity of the electron beam) is checked by the test plug, the error due to this cause will be less then 1 %

2. Since the amplitude of the triangular echo signal changes during measurement, and the slot in front of the film is adjusted so that it lies about 5 mm above the x-axis of the CRT-screen the x location of the beginning of the echo signal trace on the film is a function of the rise time and the amplitude of the signal. Since the rise time of the echo pulse in the present apparatus is about 10^{-6} sec and the echo signal magnitude usually varies between 1 and 10 cm, it can be found from simple geometric considerations that the x trace on the film might deviate about 0.07 cm on account of amplitude variations. Since the minimum x-movements recorded in mitral stenosis are about 1 cm

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to Siemens-Reiniger Werke, Erlangen, for making available to me the equipment used in this work.

The error of v is, as before, dependent on the constancy of the motor velocity in the electrocardiograph machine and may be thus estimated as better than 1 % as above

Finally because of the better resolving power of the direct writing method (200 measurements per second) the error in t will be limited to only 1 % if one assumes that t = 0.5 sec, as above.

The total error in the direct writing method is thus found to be 11 % at most, thus being appreciably better than in the photographic method. That the *total error is even less can be shown by* inserting the test plug into the reflectoscope and moving the multiple echo signals generated thereby across the left side of the CRT-screen by the potentiometer on the right hand side panel of the reflectoscope (cf. part I, page 35) In that case a step function is generated on the mingograph recording paper the step amplitude of which is independent of the distance from the zero line. It is advisable to use this calibration procedure before each measurement since the amplification-setting in the electrocardiograph machine might change during prolonged use or from day to day There is, however one source of error in the present direct writing apparatus, which may introduce a serious error in the α measurements if it is not corrected for the zero-line is not quite straight but follows the UCG curve to a certain extent. Since the distance UCG curve — zero-line is the correct value given by the 'transit time—voltage conversion apparatus, this slight error has to be corrected for in measuring the angle α.

Present investigation of the rate of movement of the anterior mitral leaflet during ventricular diastole in mitral stenosis.

In 50 cases of mitral stenosis the author has estimated the speed of movement of the anterior mitral cusp during ventricular diastole

Method.

In tracings recorded by the photographic method AM a movement-amplitude from peak E towards point A or B was measured over a period of 0.3 sec. The *average value was calculated from* measurements taken over 20 or more cardiac cycles in each patient.

Case selection.

The series consisted of 50 cases of mitral stenosis with or without an element of incompetence. All had clinical and radiological signs of mitral disease. Cardiac catheterization had been carried out in all cases. It was concluded that 45 of these cases had pure mitral stenosis with only very slight regurgitation.

Results.

As can be seen in table 2, cusp movement never exceeded a rate of 40 mm/sec. The mean value for the entire series, including all grades of mitral stenosis, was 20.1 mm/sec with 3.9 and 38.7 mm/sec as the limits of variation.

Conclusions.

The fall in tracing AM from peak E to point F in normal cases, and from peak E to points A or B in cases of mitral stenosis, represents the move-

15 Bergmann, L. Der Ultraschall und seine Anwendung in Wissenschaft und Technik. S. Hirzel Verlag Stuttgart, 1954. 6 Auflage.

16. Bickford, R. H., and Duff, R. S. Influence of ultrasonic irradiation on temperature and blood flow in human skeletal muscle. Circulation Res. 1. 534, 1953.

17 Buchtala, V Ultraschallschäden, Therapeutische Berichte. 22. 91. 1950.

18 Buchtala, V Die Schallbehandlung bei ruhendem (fixiertem) Schallkopf. In Pohlman. Ultraschalltherapie. (126)

19 Burow A. K. High intensity ultrasonic oscillations for treatment of malignant tumors in animals and man. Report of the Ac. of Science U S. S. R. (Biophys.) 106 2. 1956.

20 Burow A. K. and Andreewskaja, G. D The effect of ultrasonic oscillations of high-intensity on malignant tumors in animals and man. Report of the Ac. of Science U S. S. R. (Biophys.) 106 3. 1956.

21. Böhme, W Personal communication, 1959

22. Conte, E. and Delorenzi, E. Azione biologische degli ultrasuoni. Atti Congr naz. Radiobiol. 4. 196 1940.

23. Demmel, F Schallschäden. In Pohlman. Ultraschalltherapie (126)

24. Denier A. Ultrasonoscope in medicine. Cited by Bergmann, L. (15)

25. Denier A. Les ultrasons leurs applications au diagnostic Ultrasonoscopie et à la therapeutique Ultra-sonotherapie. Cited by Bergmann, L. (15)

26 Donald, I., Vicar J Mac and Brown, T G Investigation of abdominal masses by pulsed ultrasound. Lancet I 1188. 1958.

27 Dunn, F Physical mechanisms of the action of intense ultrasound on tissue. Am J Phys. Med. 37 148. 1958.

28. Dussik K Über die Möglichkeit hochfrequente mechanische Schwingungen als diagnostisches Hilfsmittel zu verwenden Z Neurol 174. 153 1942.

29 Dussik, K. Ultraschalldiagnostik, insbesondere bei Gehirnerkrankungen, mittels Hyperphonographie. Z. Phys. Therapie (Österr) 1. 140 1948.

30 Dussik, K., Fritsch, D J Kyriazidou, M. and Sear R. S. Measurements of articular tissues with ultrasound. Am. J Phys. Med. 37 160 1958.

31. Edler I. The diagnostic use of ultra sound in heart disease. Acta Med. Scandinav Suppl. 308 32. 1955.

32. Edler I. Ultrasound cardiogram in mitral valvular diseases Acta Chir Scandinav 111. 230 1956.

33. Edler I. and Gustafson, A. Ultrasonic cardiogram in mitral stenosis. Acta Med. Scandinav 159 85. 1957

34 Edler I. and Hertz, C. H. The use of ultrasonic reflectoscope for the continuous recording of movements of heart walls. Kungl. Fysiogr sällsk. i Lund förhandl. 24. 5 1954.

35. Edler I. and Hertz, C. H. Die diagnostische Anwendung von Ultraschall kardiogramm bei Mitralistenose. Paper read at the IV Internat. Congr on diseases of the chest of the Amer College of Chest Physicians, Köln 1956.

35 a. Edler I. and Hertz, C. H Heart diagnostics by ultrasound. Svensk Naturvetenskap 1961. Stockholm.

36 Effert, S. Der derzeitige Stand der Ultraschallkardiographie. Arch. f Kreislaufforsch. 30 213. 1959

37 Effert, S., Domanig, E. and Erkens, H. Möglichkeiten des Ultraschall-Echoverfahrens in der Herzdiagnostik. Cardiologia 34. 73. 1959

38. Effert, S., Erkens, H. and Grosse-Brockhoff Über die Anwendung des Ultraschall-Echoverfahrens in der Herzdiagnostik. Dtsch. Med. Wschr 82. 1253 1957
The ultrasonic echo m thod in cardiological diagnosis. Germ. med. Monthly 2. 325. 1957

39 Effert, S., Hertz, C. H. and Böhme, W Direkte Registrierung des Ultraschall Kardiogramms mit dem Elektrokardiographen. Z. Kreislaufforsch. 48. 230. 1959

ment of the anterior mitral leaflet from its most ventral position early in ventricular diastole to a more dorsal position. In normal cases and in other cases of heart disease without mitral involvement, this movement occurs at a speed of more than 80 mm/sec (see page 91) In mitral stenosis with, or without an element of incompetence, this movement is much slower max. 40 mm/sec. This figure accords with that reported by Effert (1959) in a series of 163 cases of mitral stenosis. Neither Effert nor the present writer have found these characteristic tracings in cases other than mitral stenosis.

SUMMARY

1 In mitral stenosis tracing AM is highly significant.
2. The dorsalward movement of the anterior cusp of the mitral valve during ventricular diastole occurs at a speed of less than 40 mm/sec.

II. RECORDING OF THE ACTION OF THE ANTERIOR LEAFLET OF THE *TRICUSPID* VALVE.

In cases of atrial septal defect, wherein the right ventricle is often dilated, the echo signal emanating from the anterior mitral cusp is found to be further removed than normal from the emission signal. In 10 such cases, aged from 18 to 53 years, the minimum distance between the anterior mitral cusp and the crystal situated over the fourth left interspace 4—5 cm from the mid sternal line, was 65 mm or more. Additional echo signals were obtained from some more ventrally and medially situated structure. This echo-source, like the mitral valve, has a quick movement with an amplitude of 17—28 mm. See Fig 16. This tracing henceforward *referred to as* T *is obtained* with the beam diverging 10—20 medially from the antero-posterior line. The minimum distance between the echo-giving structure and the crystal on the anterior chest-wall during each cardiac cycle was 31—52 mm, table 3 The corresponding maximum distance was 52—74 mm. The minimum distance was attained early in ventricular diastole, and the maximum distance during ventricular systole. If the beam-direction is altered so as to become antero-posterior echoes are received from the anterior mitral cusp too Fig 16. It is impossible to record T from the third left interspace.

In one of our cases of atrial septal defect (verified at operation) in which ECG revealed complete right bundle-branch block and the phonocardiogram showed marked splitting of the first and second heart sounds simultaneous recordings were made of tracing T and tracing AM, respectively with ECG and phonocardiogram. See Figs. 17—21. It *can be seen that the point C arrives* 0.06 sec earlier in tracing AM than in tracing T The first component of the split first sound is synchronous with C in tracing AM, and the second component is synchronous with C in tracing T The sector D—E surrounding the split second sound occurs 0.08 sec earlier in AM than in T

64. Güttner W and Pätzold J Physical properties important in human ultrasonic therapy Am. J Phys. Med. 37 219 1958.

65. Gäseler R. and Samlert, H. Zur Beurteilung des Ultraschallkardiogramms bei Mitralstenosen. Z Kreislaufforsch. 47 291. 1958.

66 Hayasi, S., Kikuchi, Y and Uchida, R. Ultraschalldiagnostik von Brusttumoren und Gallensteinen. Acta Med. techn. 9 1961.

67 Henkel Cited by Buchtala, V (17)

68. Herrick, J F Temperatures produced in tissues by ultrasound Experimental study using various technics. J Acoust. Soc. Am. 25 12. 1953.

69 Herrick, J F Baldes, E. J Haugen, M. G and Farrall, W R. Fed. Proc. Cited by Franklin et al. (42)

70. Herrick, J F and Krusen, F H. Ultrasound and medicine. A survey of experimental studies. J Acoust. Soc. Am. 26. 236. 1954.

71. Hertz, C. H. Ultraljud-ekometoden i natur teknik och medicin. Kosmos 37 78. 1959

72. Hertz, C. H. and Edler I. Die Registrierung von Herzwandbewegungen mit Hilf des Ultraschall-Impulsverfahrens. Acustica 6 361. 1956.

72 a. Hertz, C H. nd Olofsson, S. Framställning av tvådimensionella bilder med ultraljud. Paper read at the XXIV Nord. Radiolog Kongr Lund 1961

73. Higashino, S. The action of ultrasound on the neuromuscular junctions. J Cell. Comp. Physiol. 54. 251. 1959

74 Horvath, J Die morphologischen Veränderungen der Carcinomzellen nach Ultraschalleinwirkung Dtsch. med. Wschr 72 392. 1947

74 a Horvath, J Ultraschallwirkung beim menschlichen Sarkom. Strahlentherapie 75 119 1944

75. Horvath, J Experimentelle Untersuchungen über die Verteilung der Ultraschallenergie im menschlichen Gewebe. Arztl. Forsch. 1. 257 1947

76. Horvath, J Morphologische Untersuchungen über die Wirkung der Ultraschallwellen auf das Carcinomgewebe. Strahlentherapie 77 279 1948.

77 Howry D H. and Bliss, W R. Ultrasonic visualization of soft tissue structures of the body J Lab. and Clin. Med. 40 579 1952.

78. Howry D H., Stott, D A. and Bliss, W R. The ultrasonic visualization of carcinoma of the breast and other soft tissue structures. Cancer 7 354 1954

79 Howry D H., Posakony G J Cushman, C. R. and Holmes, J H. Three dimensional and stereoscopic observations of body structures by ultrasound. J App. Physiol. 9 304. 1956.

80. Hüter T F Cited by Pohlman (125)

81. Hüter T F Messung der Ultraschallabsorption in tierischen Gew ben und ihre Abhängigkeit von der Frequenz. Naturwiss. 35 285. 1948.

82. Hüter T F Physikalische Betrachtungen zur Applikation und Dosierung von Ultraschall. Arztl. Forsch. 3 585 1949

83. Hüter T F Ultraschallwellen als neue therapeutische Energieform. Artzl. Praxis 1. 2. 1949

84 Hüter T F Ballantine, H. T Jr and Coller W C. Production of lesions in the central nervous system with focussed ultrasound A study of dosage factors J Acoust. Soc. Am. 28 192. 1956.

85. Hüter T F and Bolt, R. H. An ultrasonic method for outlining the cerebral ventricles. J Acoust. Soc. Am. 23 160 1951.

86. Hüter T F and Pohlman, R. Eine optische Methode zur Bestimmung der Ultraschallabsorption in undurchsichtigen, schallweichen Medien. Cited by Pohlman (126)

87 Imig, C J Randall, B F and Hines, H. M. Effect of ultrasonic energy on blood flow Am. J Phys. Med. 33 100 1954.

Table 3.

The distance from the crystal situated on anterior chest-wall in the left fourth inter space to the anterior mitral leaflet and the structure representing echo T in 10 cases of atrial septal defect. The diagnosis was confirmed by cardiac catheterization in all cases except one (case no 10)

Case no	Age	Roentgenographic size of the heart: Volume in ml, total	Volume in ml, per square meter of body surface	sagittal diameter of the heart (cm)	Distance between crystal and echo-source: Echo T, minimum (mm)	Echo T, maximum (mm)	Echo AM, minimum (mm)	Echo AM, maximum (mm)
1	24	1430	920	12.5	35	68	82	101
2	18	920	640	10.6	36	55	70	94
3	38	1210	765	11.0	31	52	67	95
4	19	770	430	9.5	32	55	65	78
5	22	—	—	—	31	53	70	99
6	53	1450	760	12.0	43	60	67	83
7	22	1000	570	11.5	36	64	67	78
8	46	3000	1630	16.5	52	74	79	98
9	38	1900	1160	13.0	43	67	93	120
10	48	910	550	10.0	42	59	69	81

Conclusions.

T and AM have rapid movements and large amplitudes in common. It is not unreasonable therefore to conclude that they represent structures of similar type, with similar functions. T however represents a structure situated somewhat medial and caudal to the normal site of the anterior mitral leaflet. Further the structure varies between 31—74 mm from the anterior chest-wall. Having regard to localization and movement pattern, the anterior leaflet of the tricuspid valve must be regarded as the source of this echo.

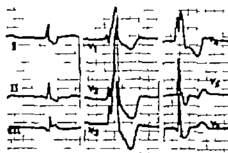


Fig 17 ECG from a case of atrial septal defect with complete right bundle-branch block, the UCG tracings from which are shown in Figs. 18—21. Paper-speed 50 mm/sec.

Further support for this conclusion is afforded by analysis of a case of complete right bundle-branch block in which the marked splitting of the first sound indicated asynchrony between the right and left ventricles (16 a) Such asynchronism between the ventricles has been demonstrated electrokymographically in 30 % of all cases of complete right bundle-branch block (18)

Comparison of these simultaneous UCG ECG and phonocardiogram recordings shows that at the time of the split first heart sound the mitral valve *cusp* begins to move about 0.06 sec before that of the tricuspid valve. At the time

112. Lynn, J G Zwemer R. L., Chick, A. J and Miller A. E. A new method for the generation and use of focused ultrasound in experimental biology J Gen. Physiol. 26 179 1942. Cited by Bergmann (15)

113. Lynn, J G et al. Focused super sonic waves in biological experiments. Electronic Eng 17 122. 1944. Cited by Bergmann (15)

114 Mundt, G H. and Hughes, W F Ultrasonics in ocular diagnosis. Am. J Ophthalm. 41. 488. 1956.

115 Nelson, P A., Herrick, J F and Krusen, F H., Temperatures produced in bone marrow bone and adjacent tissues by ultrasonic diathermy Arch. Phys. Med. 31. 687 1950

116 Nelson, P A., Herrick, J F and Krusen, F H. Ultrasonic in medicine. Arch. Phys. Med. 31. 6. 1950

117 Oksala, A. The echogram in vitreous opacities. Am. J Ophthalm. 49 1301. 1960.

118. Oksala, A. and Lethinen, A. Über die diagnostische Verwendung von Ultraschall in der Augenheilkunde. Acta Ophthalmolog. 134. 387 1957

119 Oksala, A. and Lethinen, A. Diagnosis of detachement of the retina by means of ultrasound. Acta Ophthalmolog. 35. 461. 1957

120 Oksala, A. and Lethinen, A. Diagnostics of rupture of the sclera by means of ultrasound. Acta Ophthalmolog 37 1958

121 Paul, W D and Imig, C J Temperature and bloodflow studies after ultrasonic irradiation. Am. J Phys. Med. 34. 370. 1955.

122 Pohlman, R. Die Ultraschalltherapie. Quantitative Angeben zu ihrem Wirkungsmechanismus Dtsch. Med. Wschr 73 373. 1948

123. Pohlman, R. Die Ultraschalltherapi in ihrer heutigen Entwicklung. Schweiz Med. Wschr 79 754 1949

124. Pohlman, R. Die Ultraschalltherapie Pag 43 Verlag Hans Huber Bern 1951.

125. Pohlman, R. Die Ultraschalltherapie. Pag 109—111. Verlag Hans Huber Bern 1951.

126. Pohlman, R. et al. Die Ultraschalltherapie. Verlag Hans Huber Bern 1951.

127 Pohlman, R Parow-Souchon, E. and Schlungbaum, E. Über die Temperaturverteilung im lebenden menschlichen Organismus bei Ultraschalleinstrahlung Klin. Wschr 26. 277 1948.

128. Pätzold, J and Born, H. Behandlung biologischer Gewebe mit gebundeltem Ultraschall. Strahlentherapie. 76. 486 1947

129 *Rosenberger H. Über den Wirkungs*mechanismus der Ultraschallbehandlung insbesondere bei Ischias und Neuralgien. Der Chirurg 21. 404 1950.

130 Rushmer R. F Franklin, D L. and Ellis, R. M. Left ventricular dimensions recorded by sonocardiometry Circulation Res. 4. 684 1956.

131. Satomura, S. A study on examining the heart with ultrasonics I principle II Instrument. Jap Circul. 20 227 1956

132. Satomura, S. Ultrasonic Doppler method for the inspection of cardiac functions. J Acoust. Soc. Am. 29 1181. 1957

133. Schmitt, W and Braun, H. Mitteilungen der mittels Ultraschall-Kardiographie gewonnen Ergebnisse bei Mitralvitien und Herzgesunden. Z. Kreislaufforsch. 49 214. 1960

134. Schwan, H. The biophysical basis of physical medicin J A M. A. 160 191. 1956.

135. Schwan, H. and Carstensen, E. L. Advantages and limitations of ultrasonics in medicine. J A. M. A. 149 122. 1952.

136. Schwan, H., Carstensen, E. and Li, K. Comparative evalution of electromagnetic and ultrasonic diathermy Arch. Phys Med. 35 13. 1954

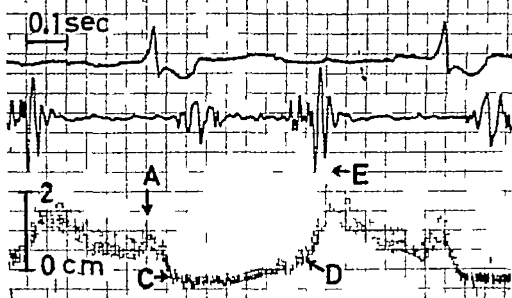


Fig 20 Action of anterior leaflet of mitral valve, recorded simultaneously with ECG and phonogram from 2nd left interspace. Same case as in Figs. 18 and 19 Crystal 5 cm from mid-sternal line in 4th left interspace Antero-posterior beam-direction. Paper speed 100 mm/sec. Th second heart sound is split. Th first component is aortic and the second is pulmonary Rise D — E begins after the aortic — but before the pulmonary component of th split second sound. Peak E occurs just after the pulmonary component.

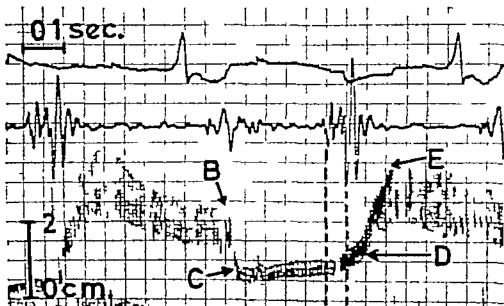


Fig 21. Action of anterior tricuspid leaflet recorded synchronously with ECG and phonogram from 2nd left interspace. Same case as in Figs. 18, 19 and 20. Crystal 2—3 cm from mid-sternal line in 4th left interspace. Beam-direction 15—20 medially Paper speed 100 mm/sec. Rise D — E begins when the pulmonary component of the second sound is maximal. Peak E occurs 0 06 sec after the pulmonary component of the second sound reaches maximal amplitude.

1. Arvidsson, H. Angiographic observations in mitral disease with special reference to volume variations in the left atrium. Acta Radiol. Suppl. Stockholm 1958.

2. Baumgarten, A. Ueber den Mechanismus durch welchen die venösen Herzklappen geschlossen werden. Arch. Anat., Phys wissensch. Med. Berlin, p. 463, 1843.

3. Cooley R. N and Sloan, R. D Radiology of the heart and great vessels. Cited by McKusick, V A. Cardiovascular sound in health and disease The Williams and Wilkins Co., Baltimore, 1958.

4. Davila, J C., Trout, R. G Summer J E. and Glover R. P A simple mechanical duplicator for cinematography of cardiac valves in action. Ann. Surg. 143.544.1956.

5. Dean, A. L. Jr The movements of the mitral cusps in relation to the cardiac cycle. Am. J Physiol. 40.206. 1916.

6 Edler I. The diagnostic use of ultrasound in heart disease. Acta Med. Scand. Suppl. 308.32.1955

7 Edler, I. Ultrasoundcardiogram in mitral valvular diseases Acta Chir Scand. 111.230 1956.

8. Edler I. and Gustafson, A. Ultrasonic cardiogram in mitral stenosis. Acta Med Scand. 159.85.1957

8 a Edler I., Gustafson, A., Karlefors, T and Christensson, B. The movements of aortic and mitral valves recorded with ultrasonic echo techniques Scientific film at IIIrd European Congress of Cardiology Roma 18—24 sept 1960

8 b Edler I Gustafson, A., Karlefors, T and Christensson B A dynamic study of the heart valves and ventricular outflow tracts using an ultrasound echo method Paper read at XXVII Nord Kongr f Inre Med. Oslo 29 6 —2 1960

9 Edler I. and Hertz, C. H. The use of ultrasonic reflectoscope for the continuos recording of the movements of heart walls. Kungl. Fysiogr Sällsk. i Lund förhandl. 24.5.54.

9 a Edler I., Hertz, C H., Gustafson, A., Karlefors, T and Christensson, B The movements of the heart valves recorded by means of ultrasound. Nord. Medic. 64. 1178.1960.

10 Effert, S., Der derzeitige Stand der Ultraschallkardiographie Arch.Kreisl. forsch. 30.213.1959

11. Effert, S Erkens, H. and Grosse-Brockhoff F The ultrasonic echo method in cardiological diagnosis. Germ. Med. Month. 2.325.1957

12. Gad, J. Klappenspiel im Ochsenherzen. Arch. Physiol. p 380.1886.

13. Gässler R. and Samlert, H. Zur Beurteilung des Ultraschallkardiogramms bei Mitralstenosen. Z. Kreislaufforsch. 47.291.1958.

14 Henderson, Y and Johnson, F E. Two modes of closure of the heart valves Heart 4.69.1912.

15 Hertz, C H. and Edler I. Die Registrierung von Herzwandbewegungen mit Hilfe des Ultraschall-Impulsverfahrens. Acustica 6.361.1956.

16 Jacobi, J Gässler R. and Samlert, H Neue Ergebnisse mit der Ultraschallkardiographie. Verh. Dtsch. Ges Kreislaufforsch. 24.295.1958.

16 a Leatham, A. Splitting of the first and second heart sounds. Lancet 2 607.1954

17 Licata, R. H. Anatomy of the heart. Cardiology An Encyclopedia of the Cardiovascular System. Vol. 1. McGraw—Hill Book Company Inc. New York, Toronto, London 1959

18. Luisada, A. A. The heart beat. New York, Hoeber 1953. Cited by Cardiology An Encyclopedia of the Cardiovascular System. Vol. 3 McGraw—Hill Book Company Inc. New York, Toronto, London 1959

SUMMARY OF PART III.

The aim of this investigation has been to determine the echo-source of tracings AM and T which are obtained from the 3rd or 4th left interspaces. Both these tracings represent structures having equally rapid motion-sequences over a distance often in excess of 20 mm.

It has been shown that

1. Tracing AM could be obtained in 77 out of 86 normal cases.
2. Tracing AM, which can be correlated to atrial activity represents the anterior cusp of the mitral valve.
3. Tracing T recordable mainly in cases of atrial septal defect, represents the anterior cusp of the tricuspid valve.

The rate at which the mitral cusps move in a dorsal direction during the atrio-ventricular emptying phase is discussed. Sources of error in angle α, which is dependant on this rate, are examined.

ERRATA.

P 38, Right column, line 7 Instead of "set up" read set-up
P 42, Fig 14, line 6 Instead of "respone" read response
P 42, Fig 14, line 10 Instead of diance read "distance
P 60 Fig 32, line 4 Instead of "the read "then
P 96, Left column, line 5 Instead of "97 mm read "98 mm
P 98, Left column, line 2 Instead of anterior" read "posterior"
P 103, Left column, line 14 Instead of "t α read "tg α"
P 106, Table 2 The values of angle α are in case no 18 12 (not 15)
case no 45 27 (not 30) case 48 17 (not 21) case 50 22 (not 25)

REFERENCES

PART ONE

1. Abramson, D I. Changes in blood-flow oxygen uptake and tissue temperatures produced by therapeutic physical agents. Am. J Phys. Med. 39 51. 1960

2. Astrom, K. E Ballantine H. T J Bell, E. and Adams, R. D An experimental neuropathological study of the effects of ultrasound on the brain of the cat. Presented at 1st Int. Congr of the Neurolog Sciences, Brussels, Belgium, July 1957

3. Bakles, E. J Herrick, J F and Stroebel, C. F Biological effects of ultrasound. Am. J Phys. Med. 37 111. 1958.

4. Ballantine, H. T J Astrom, K. E. and Bell E. Experimental lesions produced in brain and spinal cord by focused ultrasound. Presented t 1st Int. Congr of the Neurol. Sciences, Brussels, Belgium, July 1957

5. Ballantine, H. T J Bolt, R. H., Hüter T F and Ludwig, G. D. On the detection of intracranial pathology by ultrasound. Science 112. 525 1950

6. Ballantine, H. T J Hüter T F and Bolt, R. H. On use of ultrasound for tumor detection. J Acoust. Soc. Am. 26. 581. 1954.

7. Bannaski, H. and Fischer H.. Neue diagnostische Möglichkeiten des Ultraschall Impulsechoverfahrens. Med. Klin. 1953.

8. Baum, G and Greenwood, I. The application of ultrasonics locating techniques to ophthalmology Am. J Ophth. 46. 319 1958

9. Baum, G. and Greenwood, I. Ultrasound in ophthalmology Am. J Ophth 42. 249 1960.

10. Baum, G and Greenwood, I. Ultrasonography — An aid in orbital tumor diagnosis. Arch. of Ophth. 64. 180 1960.

11. Beck, W N Ultrasonic recording of the bones in a human arm J Acoust. Soc. Am. 29 865. 1957

12. Bell, E. Action of ultrasound on adult and embryonic organ systems. Am. J Phys. Med. 37 184. 1958.

13. Bender L. F Herrick, J F and Krusen, F H. Temperatures produced in bone by various methods used in ultrasonic therapy Arch. Phys. Med. 34 424. 1953.

14. Bender L. F Janes, J M. and Herrick, J F Histological studies following exposure of bone to ultrasound. Arch. Phys. Med. 35. 555. 1954.

Bjurström & Co Boktryckeri
Ystad 1961

40. Fischer E. Basic biological effects of ultrasonic energy Am. J Phys. Med. 33 174 1954

41. Fischer E White, E. A., Hendricks, S. L. Jr Chevalier B. A. and Chevalier R. B. Effect of moderate and of weak ultrasonic exposures upon normal and denervated mammilian muscle. Am. J Phys. Med. 33, 281, 1954.

42. Franklin, D L., Ellis, R. M. and Rushmer R. F Aortic bloodflow in dogs during treadmill exercise J Appl. Physiol. 14. 809 1959

43. French, L. A., Wild, J J and Neal, D Detection of cerebral tumors by ultra sonic pulses. Pilot studies on post mortem material. Cancer 3. 705. 1950

44. French, L. A. and Wild, J J J Amer Cancer Soc. March 1951. Cited by Wild, J J and Neal, D (142)

45 French, L. A., Wild, J J and Neal, D. Attempts to determine harmful effects of pulsed ultrasonic vibrations. Cancer 4. 342. 1951.

46. Frucht, A. H. Die Schallgeschwindigkeit in menschlichen und tierischen Geweben, Z. ges. exper Med. 120 526. 1953.

47 Fry W J Mechanism of acoustic absorption in tissue. J Acoust. Soc. Am. 24. 412. 1952.

48. Fry W J and Dunn, F Ultrasonic irradiation of the central nervous system at high sound levels. J Acoust. Soc. Am. 28. 129 1956.

49 Fry W J Tucker D Fry F J and Wulff, V J Physical factors involved in ultrasonically induced changes in living systems. J Acoust. Soc. Am. 23. 364. 1951.

50. Fry W J Wulff, V J Tucker D. and Fry F J Physical factors involved in ultrasonically induced changes in living systems. J Acoust. Soc. Am. 22. 867 1950.

51. Gersten, J W.. Thermal and non-thermal changes in isometric tension, contractile protein in frog muscle by ultrasonic energy Arch. Phys. Med. 34. 675 1953.

52. Gersten, J W.. Changes in hydration of muscle and tendon following th application of ultrasonic energy Arch. Phys. Med. 36. 140 1955.

53. Gersten, J W Muscle shortening produced by ultrasound. Arch. Phys. Med. 38. 83. 1957

54 Gersten, J W.: Non-thermal neuro-muscular effects of ultrasound. Am. J Phys. Med. 37 235. 1958.

55. Gersten, J W and Kavashima, E. Changes in phosphocreatine produced in striated muscle by ultrasound. Am. J Phys. Med. 33 207 1954.

56. Gohr H. and Wedekind, Th. Der Ultraschall in der Medizin. Klin. Wschr 19 25. 1940.

57 Goldman, D E. and Hüter T F Tabular data of the velocity and absorption of high-frequency sound in mammalian tissues. J Acoust. Soc. Am. 28 35. 1956.

58. Goldman, D E. and Richards, J R. Measurements of high-frequency sound velocity in mammalian soft tissues. J Acoust. Soc. Am. 26. 981. 1954.

59 Gordon, D Echoencephalography Ultrasonic rays in diagnostic radiology Brit. Med. J I. 1500. 1959

60 Grabar P and Prudhomme, P O Di mechanischen und chemischen Wirkungen der Ultraschallwellen. Kongressbericht der Erlanger Ultra schall-Tagung 1949 S. Hirzel, Zürich. 114. 119

60 a. Gurevic, M. D and Sobakin, M. A. Some viewpoints on the use of ultra sound in diagnosis of internal disorders Vrasojuru, naucnoisl. inst. med. instrumentov i oborndovanija. 4. 1960.

61. Gustafson, A. Personal communication. 1956.

62. Güttner W Di Energieverteilung im menschlichen Körper bei Ultraschall-Einstrahlung. Acustica 4. 547 1954.

63. Güttner W Fiedler G. and Pätzold, J Über Ultraschall-abbildungen am menschlichen Schädel. Acustica 2. 148. 1952.

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88 Jacobi, J Gläsler R. and Samlert, H. Neue Ergebnisse mit der Ultraschallkardographie. Verh. Dtsch. Ges. Kreislaufforsch. 24 293 1958

89 Jeppsson, S. Echoencephalography III. Further studies on the sources of the midline echo and a clinical evaluation. Acta Chir Scandinav 119 455. 1960.

90 Jeppsson, S. Echoencephalography IV The midline echo. An evaluation of its usefulness for diagnosing intracranial expansivities and an investigation into its sources. Acta Chir Scandinav Suppl. 1961.

91. Kalmus, H. P Electronic flowmeter system. Rev Sc. Instr 25. 201. 1954. ref in Kelly- Ultrasound by Baldes et al. pag 166.

92. Keidel, W D Über eine Method zur Registrierung der Volumänderungen des Herzens am Menschen. Z. Kreislaufforsch. 39 257 1950.

93. Keidel, W D Diagnostische Anwendungsmöglichkeiten des Ultraschalls in der physiologischen Methodik. Cited by Effert, (36)

94. Kichuchi, Y Uchida, R., Tanaka, K. and Wagai, T.. Early cancer diagnosis through ultrasonics. J Acoust. Soc. Am. 29.824. 1957

95. Koeppen, S. Die Anwendung des Ultraschalls in der Medizin. Hippokrates Verlag. 1951 23 and 61.

96. Koeppen, S. Present status of the clinical pplication of ultrasonic therapy Am. J Phys. Med. 37 127 1958.

97 Krusen, F H. Gegenwärtiger Stand der Anwendung von Ultraschall-Energie in der physikalischen Medizin. Southern Med. J 45 55 1952.

98. Lehmann, J.. Beitrag zur Ultraschall hamolyse. Strahlentherapie 79 533. 1949.

99 Lehmann, J The biophysical mode of action of biologic and therapeutic ultrasonic reactions J Acoust. Soc. Am. 25. 17 1953.

100 Lehmann, J The biophysical basis of biological ultrasonic reactions with special reference to ultrasonic therapy Arch. Phys. Med. 34. 139 1953.

101. Lehmann, J The present status of ultrasonic therapy Arch. Phys. Med. 34. 741. 1953.

102. Lehmann, J and Biegler R. Changes of potentials and temperature gradients in membranes caused by ultrasound Arch. Phys. Med 35. 287 1954.

103. Lehmann, J and Herrick, J F Biological reactions to cavitation, a consideration for ultrasonic therapy Arch. Phys. Med. 34. 86 1953.

104 Lehmann, J nd Krusen, F H. Biophysical effects of ultrasonic energy on carcinoma and their possible significance. Arch. Phys. Med. 36. 452. 1955.

105. Leksell, L.. Echoencephalography I. Detection of intracranial complications following head injury Acta Chir Scandinav 110 301. 1955.

106. Leksell, L. Echoencephalography II. Midline echo from the pineal body as an index of pineal displacement. Acta Chir Scandinav 115. 255 1958.

107 Lithander B. A control method for echoencephalography Acta Psych. et Neurol. Scandinav 35. 235 1960.

108. Lithander B. The clinical use of echoencephalography Acta Psych. et Neurol. Scandinav 35. 241.1960.

109 Ludwig, G D The velocity of sound through tissues and the acoustic impedance of tissues. J Acoust. Soc. Am. 22. 862. 1950

110 Ludwig G D and Struthers, F W.. Considerations underlying the use of ultrasound to detect gallstones and foreign bodies in tissue. Project No. NM 004 001, Report No. 4. United States Naval Medical Research Instit. Bethesda, Md., 1949 Cited by Herrick and Krusen (70)

111. Lynn, J G., Zwemer R. L. and Chick, A. J The biological application of focused ultrasonic waves. Science 96. 119. 1942. Cited by Bergman (16)

137 Thelaman, H. and Pfander F Über die Durchlässigkeit des Knochens für Ultraschall. Strahlentherapie 80 607 1949

138. Vlieger M. de and Ridder H. J Use of echoencephalography Neurology 9 216 1959

139. Wakins, K. Ultrasonic Energy as applied to medicine. Am. J Phys. Med 32. 32. 1953.

140. Wild, J J The use of ultrasonic pulses for the measurement of biological tissues and the detection of tissue density changes. Surgery 27 183. 1950.

141. Wild, J J Crawford, H. D and Reid, J M. Visualization of the excised human heart by means of reflected ultrasound or echography Am. Heart J 54. 903. 1957

142. Wild, J J and Neal, D Use of thigh frequency ultrasonic waves for detection changes of texture in living tissues. Lancet 260. 655. 1951.

143. Wild, J J and Reid, J M. Further pilot echographic studies on the histological structure of tumors of the living intact human breast. Am. J Pathol. 28. 839 1952.

144 Wild, J J and Reid, J M. Application of echo-ranging techniques t the determination of structure of biological tissues. Science 115. 226 1952.

145. Wild, J J and Reid, J M. The effects of biological tissues on 15-mc pulsed ultrasound. J Acoust. Soc. Am. 25. 270. 1953.

146. Wild, J J and Reid, J M. Diagnostic use of ultrasound. Brit. J of. Phys. Med. 19 248. 1956.

147 Wood, R. V and Loomis, A. L. Physical and biological effects of high-frequency sound-waves of great intensity Phys. Rev 29 373. 1927

148. Yoshida, T Mori, M., Nimura, Y Okimura, M., Hikita, G., Nakanishi, K. and Satomura, S Study on examining the heart with ultrasonics III Kinds of Doppler beats IV Clinical application. Jap Circ. J 20 228. 1956.

149 Yoshida, T Mori, M., Nimura, Y Hikita, G., Takagishi, S., Nakanishi, K. and Satomura, S. Analysis of heart motion with ultrasonic Doppler method and its clinical application. Am. Heart J 61. 61. 1961.

PART TWO

1. Edler L and Hertz, C. H.. Kungliga Fysiografiska Sällskapets i Lund för handlingar Bd. 24 Nr 5. March 10 1954.

2. Edler L and Gustafson, A. Acta Med. Scandinav 159.85 1957

3. Effert, S., Erkens, H. and Grosse-Brockhoff, F Dtsche med. Wschr 8 1253 1957 Germ Med. Monthly 2.325.1957

4 Effert, S. and Domanig E. Dtsche med. Wschr 84.6.1959 Germ. Med. Monthly 4.1.1959

5 Edler L Cardiology An Encyclopedia of the Cardiovascular system. Suppl. In press.

6. Edler L Acta Med. Scandinav Suppl. 308.32.1955

7 Mc Millan, I. K. R., Daley R. and Matthews, M. B Brit. Heart J 14. 42 1952.

8 Davila, J C., Trout, R. G Sunner J E. and Glover R. P.. Annals of Surgery 143.544.1956

9 Effert, S., Hertz, C. H. and Böhme, W Z. Kreislaufforschg. 48.230.1959

10. Edler L Acta Med. Scandinav Suppl. 370.1961.

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19 McMillan, I. K. R., Daley R. and Matthews, M. B. The movement of aortic and pulmonary valves studied post mortem by colour cinematographic. Br Heart J 14 42.1952.

20. McMillan, I. K. R. Aortic stenosis. A post mortem cinephotographi study of valve action. Br Heart J 17.56 1955.

21. O'Malley C. D and Saunders, C. M Leonardo da Vinci on the human body Henry Schuman, New York 195..

22. Pernkopf, E. Topographische Anatomie des Menschen. 2te unveränd. Aufl. I Band II Hefte. Urban & Schwarzenberg Berlin, Wien 1943.

23. Rushmer R. F Finlayson, B. L. and Nash, A. A.. Movements of the mitral valve. Circ. research 4.337.1956.

24. Schmitt, W and Braun, H.. Mitteilungen der mittels Ultraschallkardiographie gewonnenen Ergebnisse bei Mitralvitien und Hertzgesunden. Z. Kreislaufforsch. 49.214.1960

25. Smith, H. L., Essex, H E and Balder E. J A study of the movements f heart valves and of heart sound Ann. Int. Med. 33.1357.1950

26. Vangensten, O Fonahn, A and Hopstock, H Quaderni d'Anatomia I—IV Christiania, Casa editrice Jacob Dybvad. 1911, 1912, 1913, 1914

27 Virchow H. Ein nach Form zusammengesetztes Thorax-Skelett zu Demonstration der Lage der Ebenen der Herzklappen. Berliner Klin. Wschr 9 441.1908.

28. Virchow H. Ein nach Form zusammengesetztes Thora. -Skelett zur Demonstration der Lage der Ebenen der Herzklappen sowi einiger anderer anatomisch und klinisch wichtiger Verhältnisse. Arch Anatomi p. 15? 1913

29 Yoshida, T Mori, M., Nimura, Y Hikita, G Takagishi, S., Nakanishi, K. and Satomura, S. Analysis of heart motion with ultrasonic Doppler method and its clinical application. Am. Heart J 61.61.1961

CONTENTS

than hydrochloric acid which may affect iron absorption from food. Patients treated with partial gastrectomy show a good absorption of iron salts, but poor absorption of iron from food. It may be assumed that either normal motility of the gastrointestinal tract or some factor other than the hydrochloric acid of the gastric juice is necessary for normal absorption.

Absorption of iron from food may also be disturbed by a high phosphate content in the food and also by the phytate content as they tend to form insoluble iron salts. A low-phosphate diet again increases absorption. An increase of ascorbic acid in the food accelerates absorption and so does the addition of copper to the diet. Earlier the general opinion was that the ferritin content of the mucous membrane of the small intestine regulated iron absorption in the intestines. It was believed that the absorption of iron was inhibited if the ferritin content was high, and thus gave rise to concepts such as »mucosal block». Investigations with radioactive iron (Fe) have shown, however that no such physiological mechanism regulating iron absorption exists. Research workers are of the opinion that the old phrase mucosal block» should be discarded until the factors regulating iron absorption have been clarified.

Investigations with radioactive iron have revealed that normal adults absorb less than 10 per cent of the iron contained in food. When the iron requirement is greater as e.g. in children and in iron deficiency anaemias, the amount absorbed is at least doubled, and even 40 per cent. In a daily diet containing 10—15 mg a maximum of 1—1.5 mg is absorbed by normal persons daily. For men this fully compensates for the daily loss of iron, but in women growing children and cases of haemorrhage an iron deficiency state may ensue.

If the daily deficit is only 0.5—1 mg it takes several years before an iron deficiency state emerges. If the daily diet contains less iron than the staple diet iron deficiency may develop considerably sooner the same is true in connection with even small persistent haemorrhages. Abnormally profuse menstruation, 100—150 ml a day increases the loss of iron by 2—3 mg per day and soon results in an iron deficiency. It should be noted that iron deficiency may exist in the organism for a long time without any noticeable fall in the haemoglobin content.

ACTA MEDICA SCANDINAVICA

SUPPLEME[NT]

IRON DEFICIENCY IN THE FINNISH POPULATION

BY
VILJO ANTILA

ACCOMPANIES VOL. 173

HELSINKI 1962

EARLIER INVESTIGATIONS

1 Haemoglobin (Hb)

The first important haemoglobin investigation in Finland was that made by Becker (1915) into the blood picture of fish tapeworm carriers. A selected control series of healthy subjects is attached to the investigation.

Tötterman (1949) has assembled the studies following Becker's investigation into »1915–1946 material». He has calculated the mean values of all these studies, those of the »1915–1946 material» and of his own series (Table 1). The mean values thus obtained for Finnish men were 13.6 and 13.3 g/100 ml and for Finnish women 12.1 and 12.1 g/100 ml.

In the same year Setälä (1949) examined the haemoglobin value of the blood of the inhabitants of Kärkölä, a parish in South Finland. In this very extensive series, comprising 697 women and 458 men ranging in age from 20 to 59 years, Setälä obtained a mean haemoglobin value of 13.4 g/100 ml for men and 12.1 g/100 ml for women. These mean values agree almost precisely with those quoted by Tötterman and with the material published in 1944 by Turpeinen who quoted a mean [illegible] of 13.6 g/100 ml for men and 12.1 g/100 ml for women. Harjola (1946) quotes [illegible] of 12.0 g/100 ml for women. The values from Pätiälä's (1951) material, 13.3 g/100 ml for men and 12.2 g/100 ml for women, are roughly the same.

No important study of the haemoglobin values in the adult population in Finland has been undertaken in the last ten years.

Literature on the haemoglobin level is very extensive, and accordingly the Finnish studies will here be compared mainly with corresponding studies carried out elsewhere in Scandinavia. A few papers of interest from other countries will also be mentioned.

Tötterman has found that the haemoglobin values in Finland are generally lower than in the other Scandinavian countries. This is clearly evident from a comparison of Tables 1 and 2, the latter listing Scandinavian papers; statistical treatment would obviously demonstrate quite significant differences. Whether or not these differences arise from the incomplete standardization of Finnish haemometers, as suggested by Tötterman, is a question which will not be discussed here.

In Table 3 both large series of an older date and more recent studies from a few European countries and the USA have been collated. The most recent studies

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Table 3. Haemoglobin (g/100 ml) studies in various countries

Year	Authors	Men			Women		
		Number	Mean value	Age	Number	Mean value	Age
1945	Hurtado & al. (compiled from materials in various countries)	7110	15.4	adults			
1946	Milam & Muench, USA	611	14.3	over 12 yrs.	838	12.9	over 12 yrs.
1948	Pett & Ogilvie, Canada	221	14.1	20–79	329	12.6	20–79
1951	Chaloupka & al., USA				275	13.2	17–49
1952	Berry & al., Great Britain	245	15.8	adults	266	13.9	adults
1954	Hawkins & al., Canada	377	14.1	21–98	326	13.0	21–91
1956	Morris & al., USA	1000	16.4	15–49	1000	14.3	15–49
1958	Judy & Price, USA				663	12.6	11–69
1958	Marides & Michael-Karageorgopoulou, Greece	842	15.5	18–60	365	14.1	18–60
1959	Ecklebe, Western Germany	500	15.5	20–59	500	13.3	20–59
1961	Kilpatrick & Hardisty (Rhondda), Great Britain	600	14.9	35–65	200	13.3	35–64
1961	Kilpatrick, (Wensleydale) Great Britain	182	14.1	35–65	230	13.0	35–64

have been carried out mainly by the cyanmethaemoglobin method employed in the present study or by the oxyhaemoglobin method.

The mean values in Table 3 vary considerably primarily dependent on the basis on which the material was selected, though age distribution also has its importance in extensive series. It should also be noted that some of the studies were carried out by modern methods and others by methods of an older date, another reason for divergences. (The mean values in Tables 1, 2 and 3 have, where the author has indicated the mean value as a percentage, been converted into g/100 ml according to the standard indicated by the author.)

Table 4. Finnish serum iron (γ %) studies

Year	Authors	Men			Women		
		Number	Mean value	Min. max.	Number	Mean value	Min. max.
1940	Hirvonen	25	140		25	119	
1946	Harjola				9	95	67–127
1949	Totterman	67	141	88–276	66	122	70–202
1953	Fredriksson	18	143	82–220	25	124	62–201

(All mean values in the table are given to the nearest integer.)

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2 Serum iron level (SeFe)

Four studies of serum iron levels have so far been carried out in Finland (Table 4). The most valuable of these is that by Tötterman on a series consisting of nurses, medical students and other subjects found healthy on examination. The series was relatively large: 66 adult women and 67 men but since the material was selected it provides no picture of the general serum iron level among the Finnish population. The results should be taken primarily as comparable normal mean values.

In an earlier series of selected hospital *patients (Hirvonen 1940) and a later con*trol series by Fredrikson (1953) the results for both men and women are of the same magnitude as those in the study by Tötterman. These values, therefore, are probably equal to the normal mean values of a healthy Finn. A somewhat lower mean value was obtained by Harjola for his series of nine healthy women, but this may be attributable either to the method employed or to the limited range of the material. On the basis of the first three studies, the mean value obtained for Finnish men is 141 γ % and women 122 γ %.

Compared with the studies published in the other Scandinavian countries (Table 5) these mean values approach very nearly those obtained by the Swedish Vahlquist (1941) Lundström (1949) and Hagberg (1953). They are considerably higher than those obtained by other Scandinavian authors. Skouge (1939) of *Norway reports a mean value of 118 γ %* for men and 104 γ % for women. Hoyer (1946) of Denmark, respectively 131 γ % and 115 γ %. Rustung (1949) also of Denmark, 120 γ % and 102 γ %. The mean values obtained by other Swedes (Waldenström 1946, Lövgren 1945, Laurell 1947, Nilsson 1948, Andersson 1950) are

Table 6. Earlier TIBC (γ %) studies

Year	Authors	Men			Women		
		Number	Mean value	Min.-max.	Number	Mean value	Min.-max.
1947	Laurell, Sweden	61	315	254–406	39	315	245–395
1949	Cartwright & Wintrobe, USA	15	347	306–396	15	371	316–429
1949	Rath & Finch, USA	15	311	254–437	15	288	224–415
1951	Ventura & Klopper, Great Britain				25	328	11–430
19[illegible]	Braunsteiner & al., Western Germany	17	343		8	352	
1952	Da[illegible]es & al., Great Britain	20	304	249–387	20	320	201–429
1[illegible]5[illegible]	[illegible]dow & Bevers, USA	10	341	253–388			
1953	Brend[illegible]trup, Denmark	20	311		20	309	
1953	H[illegible]g[illegible]erg, Sweden	26	371		28	338	
19[illegible]3	Mukherjee & Mukherjee, India				50	338	290 376
19[illegible]5	Rech[illegible]berg, Western Germany	86	309		78	307	
1937	Stengl & Schade, USA	10	253	184 337	10	250	213–306
19[illegible]	Verloop & al., Netherlands	70	348	278 401	20	343	247–411

PREFACE

My respected teacher, head of the Adults' Epidemic and Medical Departments of the Aurora Hospital, Professor Erkki Klemola, M.D., suggested to me this theme. In the course of my investigation he gave me valuable advice and inspired me. For all this I express my sincere thanks.

Favourable consideration towards this work was shown by the head of the Finnish Red-Cross Blood Service, H. R. Nevanlinna, M.D., and the head of the Physiological Department of the Institute of Occupational Health, Martti Karvonen, Ph.D., (Oxon.), who have spared no pains in guiding and advising me both on the haematological problems and the field work phase. I am greatly indebted to them.

My best thanks are due to the head of the First Medical Clinic of Helsinki University Central Hospital, Professor Pentti I. Halonen, M.D., for valuable advice and for the support he has given me in the various stages of my investigations.

I also thank the numerous persons who in the parishes of Ilomantsi and Pöytyä, in Uusimaa Jäger Battalion and in the Helsinki Nurses Training School have helped me in many ways. Furthermore I am very grateful to those who assisted me in collecting literature, with the laboratory work, statistical treatment of the material and drawings, and to those who translated my paper. I specially wish to thank Miss Marja Pietilä for the many ways in which she helped during the investigation.

Those who volunteered to submit to the examination should not be forgotten. They did so despite the inconvenience involved simply in getting to the place of examination. My gratitude is due to all of them.

The investigation was made possible by the economic support granted by the Association of Social Hygiene and the Pharmaceutical Manufacturers Orion Oy. I am greatly indebted for this assistance.

Helsinki, October 1962

V. A.

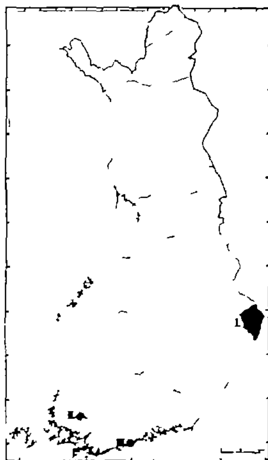
PRESENT INVESTIGATION

Series

The series consisted of 464 individuals examined in 1959 in the parish of Ilomantsi and 442 individuals examined in the parish of Pöytyä. These parishes were selected, first because the examination was intended to cover the population of an East Finnish and a West Finnish parish and second census lists compiled the previous year for an investigation into heart diseases in Finland were available for these parishes. The first phase of the *study took place in Ilomantsi from Feb.* 12 to 20 1959 and in Pöytyä from March 5 to 16 1959 A control examination, to verify the effects of iron treatment, was carried out in Ilomantsi from June 12 to 18 1959 and in Pöytyä from July 2 to 13 1959

Ilomantsi lies in the easternmost part of Finland. It is 1101.5 square miles in area (see map) According to the census of 1958, which was taken as the source for population statistics, there were 14127 inhabitants. Pöytyä lies in South-West Finland (see map) and is 123 05 square miles in area. According to the 1958 census, the parish had a population of 5074

The 1958 census lists gave the following occupational distribution for the population of these two parishes



Map of Finland I The parish of Ilomantsi Eastern Finland
II The parish of Pöytyä, Western Finland
III Helsinki

INTRODUCTION

The several extensive general surveys of iron metabolism (e.g. Laurell 1952 and Demulder 1958) and two important monographs, Iron in Clinical Medicine (1958) and Eisenstoffwechsel (1959) that have been published in recent years make it unnecessary to go into the details of iron metabolism. Only the essential factors considered in the above sources and affecting the results of the present investigation are reported on in brief here.

The average adult male has some 4—5 g iron in his body to be exact, a normal person weighing 70 kg has 4.2 g of iron. Of this amount 2—3 g, some 70 per cent, is bound with haemoglobin, 1—1.5 g or some 23.5 per cent with the iron stores of the body ferritin and haemosiderin. The remainder is bound with myoglobin, respiratory enzymes, and plasma, or occurs in some unknown form.

The breakdown of red cells liberates 20 mg of iron daily which the organism stores and re-utilizes for red cell formation. A man loses or excretes 0.5 1.5 mg iron daily According to chemical studies, some 0.2 mg/day and according to studies carried out with radioactive iron, 0.33—0.52 mg/day is removed in the faeces. In addition to this iron, mainly deriving from disintegrated mucosal cells and the bile, iron is also removed through perspiration and hair growth. Women lose, additionally through menstrual blood flow (35—70 ml) 16—32 mg of iron during the cycle equalling some 0.5—1 mg/day

This loss of iron must be replaced by iron contained in the diet. The ordinary occidental diet contains 10—15 mg per day the Finnish staple diet, according to Turpeinen (1944) and Pekkarinen (1962) has the same iron content.

The iron in food is usually in the form of colloidal ferric hydroxide which is reduced to ferrous iron in the stomach. Iron is best absorbed in ferrous form, as has been shown in investigations made with radioactive iron. The absorption takes place mostly in the duodenum near the pylorus partly in the stomach and the more distal parts of the small intestine.

It is believed that the gastric hydrochloric acid plays an important role in iron absorption as it changes ferric compounds into ferrous compounds. It has been shown experimentally however that the absorption of iron from food is not reduced in subjects with achlorhydria, nor has administration of hydrochloric acid to such subjects increased absorption. Many investigations show that there are in the digestive tract other local secretory factors

These people were sent a letter briefly describing the purpose of the investigation and inviting participation. News of the investigation was simultaneously published in the local papers. Of those who had received the invitation, the following numbers came for an examination

		Men	Women	Total
Ilomantsi		219	245	464
	per cent	79.6	89.1	84.4
Pöytyä		199	243	442
	» »	72.4	88.4	80.4
Total		418	488	906
	» »	76.0	88.7	82.3

The distribution by age groups of those attending examination was the following

	20–29	30–39	40–49	over 50
Ilomantsi[1])				
men, on census list	1221	918	795	1023
» attending examination	58	50	58	53
women, on census list	1008	849	732	1154
» attending examination	42	68	58	77
Pöytyä				
men, on census list	393	269	361	476
» attending examination	33	51	57	58
women, on census list	393	325	360	627
» attending examination	51	65	57	70

The second part of the series consisted of 53 national servicemen and 44 student nurses examined in Helsinki.

The national servicemen, whose ages ranged from 18 to 23 years, had started service 6 weeks before the investigation began. Both at the earlier medical examination on drafting and at the examination on entering the army these men had been found to be in good health. Most of them came from the province of Uusimaa. By civilian occupation, 12 were heavy manual workers, 29 light manual workers and 12 intellectual workers, mostly students. For the six weeks preceding the examination they had undergone basic infantry training during which time they had been vaccinated against the most common infectious diseases and smallpox.

The ages of the student nurses ranged from 19 to 23 years. They came from different parts of Finland and had started their training course three months before this investigation began. When applying for admission to the school of nursing they had to produce a medical certificate, and on entering the school they were examined by the school doctor. All had been found healthy in both examinations. During the first three months of their training they studied at the Nurses Training School (a

[1]) The Ilomantsi group of 20–29 included 5 men and 2 women under 20. They appeared for the examination without being invited, and the error was not detected until the final treatment of the results. Their elimination from the series would have required a great deal of additional work and was considered unnecessary since the groups of national servicemen and student nurses also included individuals under 20 years of age.

THE PURPOSE OF THE INVESTIGATION

The purpose of the in estigation was to study whether iron deficiency was common among the population of Finland and to determine its distribution but not to determine the normal haemoglobin value nd serum iron level in healthy subjects. To this end, a study was made of the haemoglobin value, serum iron level and the iron-binding capacity of the serum of the blood of rural population in Finland and of a group of selected, healthy young people from different parts of the cou try

W th the results obtained, an attempt was made to find out whether the selected series differed from the rural population and whether any difference was discernible between the parish of Ilomantsi in Eastern Finland and that of Pöytyä in Western Finland.

From the differences noted between the results, an attempt was then made to establish whether the total calorie consumption, marital status and parity had affected these results. Th nfluence of the staple Finnish diet, both unfortified and with added iron, has also been studied

earliest, half an hour after the sample had been drawn. Each specimen was determined in dupl cate, and the result is the mean value of the determinations. I few cases single determination had to be accepted because of tube breakage The specimens were taken and measurements carried out by the same nurse throughout the investigation.

3. Determination of serum iron

Taking and storage of blood specimens

The blood specimens were draw mainly by the writer in person during short term stays by V2A stainless steel cannulae which, according to several earlier investigat ons (Heilmeyer & Plotner 1937 Brochner Mortensen & Olsen 1940, Vahlquist 1941) cause no impurity and give reliable serum iron levels.

Af er the specimens had remained for 1—2 hours in a covered centrifuge tube they were centrifuged in the place of examination, and the serum was pipetted immediately af er centrifuging The sera were stored in refrigerator t the place of investigation and after the field work had been completed they were transported to Helsinki. I the clinical laboratory of the Aurora Hospital they were kept t temperature below 0°C until the day of examination when the sera were defrosted t room temperature and the determinations made on serum at room temperature The analyses were carried out 1 week to 6 months after the taking of specimens, the clinical laboratory of he Aurora Hospital or the Physiological Department of the Institute of Occupational Health in Helsinki.

The centrifuge tubes and pipettes employed for the examination were treated as follow af er routine laboratory washing they were placed for 24 hours in concentrated nitric acid solution. The tubes were then washed three times in iron-free ion exchange w ter The washed tubes were dried in hot-air cupboard.

The method

The method employed for determination of serum iron was that described by Schales (1958) which was based on methods described by Heilmeyer & Plotner (1937) and modified by Schales (1939) and Barkan & Walker (1940)

The principle of the method

The serum iron is brought into dialyzable form by the addi n of hydrochloric acid t the serum. Pr eins are precipitated by trichloracetic acid. The lea solution obtained is reduced by sodium aceta and hydroquinone \ colour reagent, o-phenanthroline is added to giv pink colour

The analysis

- ml of serum is pipet ed into centrifuge tube
- 1 ml of 0.33 N h d hloric acid is added, the tube is shaken and lef to stand for an hour
- 1 ml of 20 % trichloracetic acid is added, the t be shaken and left to stand for 15 min.
- Centrifuged for about 15 min. t 2000 RPM.
- 2 ml of the clear supernatant is pipetted into a test tube.
- 0.25 ml of 50 % sodium acetat solution is added, and the tube is shaken.
- 0.15 ml of 1 % hydroquinone solution is added and the tube is shaken.
- 0.5 ml of 0.1 1 10-phenanthroline solution is added, and the tube is shaken.
- The tube is left to stand until the pink colour has fully developed (about 20 min.).
- Measured in 10.0 mm curett by Beckman DU spectrophotometer t wav length of 510 µm against redistilled water The blind alue is determined using 2 ml redistilled water instead of serum.

4. Determination of the iron-binding capacity of the serum

The method published by Peters et al. (1956) was employed t determine the total iron-binding capacity of the serum.

The principle underlying the method is that the serum to be examined is saturated by ferrous iron, and the serum iron not bound by protei is eliminated with anion exchange resin. The iron content of the resulting filtrate is then determined by the ordinary iron determination method.

The analysis

- 1 ml of serum is pipetted into centrifuge tube.
- 0.1 ml ferric ammonium citrate containing 5 micrograms of iron is added. The tube is allowed to stand for about 10 min. t room temperature
- 0.4 ml of dry resin (Amberli IRA 410 British Drug Homes, Ltd.) is added and stirred for 5—10 min.
- 5 ml of buffer solution of pH 7.5 containing 0.11 M NaCl and 0.04 M barbital, is added and stirred for several minutes.
- Centrifuged at the ra of 2000 RPM for 10 min.
- 5 ml of lear supernatant is pipetted and the iron determination carried out.

Since it was more practical to carry out also he iron determination connected with the capacity determination by the iron determination method described by Peters et al. (1956) this method was employed. Its underlying principle and the course of the analysis are as follows

The iron contained in the serum to be studied is brought into dialyzable form by adding hydrochloric acid to the solution. The liquid obtained is reduced by means of thioglycolic acid. Proteins are precipitated by trichloracetic acid, after which the supernatant is neutralized by sodium acetate using bathophenanthroline as colour reagent.

Table 1 Earlier Finnish haemoglobin (g/100 ml) studies concerned with adults

Year	Authors	Men			Women		
		Number	Mean value	Min. max.	Number	Mean value	Min. max.
1915	Becker	22	12.8	11.5–14.8	18	11.6	10.9–12.6
1919	Appelberg	11	14.4	13.0–15.5	11	12.0	11.2–13.2
1925	Lindström & Tallqvist	33	13.5	13.1–14.5	33	12.0	11.0–12.4
1939	Forsell	10	14.0	13.5–14.9	10	12.4	11.7–13.2
1939	Totterman, G	11	14.2	13.4–14.9	11	12.5	11.7–13.5
1943	V rkk nen	10	13.7	11.9–15.0	10	11.9	11.2–12.4
1944	Turpeinen	94	13.8		82	12.1	
	1915 1946 material"	109	13.6		109	12.1	
1946	Boström	10	13.2	11.6–14.8	14	12.6	11.3–13.9
1946	Harjola				15	12.0	
1949	Setälä	458	13.4		697	12.1	
1949	Tötterman, L.	67	13.3	12.0–15.7	66	12.1	11.2–13.4
1951	Patiala	50	13.3	11.2–14.8	50	12.2	10.7–14.4

Table 2. Scandinavian haemoglobin (g/100 ml) studies concerned with adults

Year	Authors	Men			Women		
		Number	Mean value	Min. max.	Number	Mean value	Min. max.
1933	Werdinius, North Sweden	722	12.4		962	11.1	
1933	Werdinius, South Sweden	530	13.2		498	12.2	
1934	Jervell & Waaler Norway					16.2	
1935	Linneberg & Schartum-Hansen, Norway	51	15.6	14.2–18.4	60	14.1	12.1–17.1
1936	Bierring & Sørensen, Denmark	60	15.0	13.2–17.0	60	13.5	11.4–16.0
1938	Bratt, Norway	50	15.5		50	13.4	
1939	Skouge, Norway	50	14.9	13.1–16.4	50	13.5	12.3–14.9
1941	Vahlquist, Sweden				50	13.5	
1943	Brøchner Mortensen, Denmark	50	14.9	12.8–17.2	50	13.3	11.7–15.7
1944	Vahlquist & Neander (1939) Sweden	50	15.7		50	13.5	
	Vahlquist & Neander (1943) Sweden	40	15.4		40	13.1	
1946	Kaada, Norway	2000	14.9		1000	13.0	
1948	Andersen & Norman, Denmark	2956	14.2		2018	12.7	
1948	Nilsson, Sweden	68	14.0		66	12.7	
1949	Rustung, Denmark	19	14.1	12.4–15.5	24	13.1	11.5–15.5
1950	Andersson, Sweden	20	15.6	13.3–17.0	50	13.8	11.6–17.5
1950	Lundstrom, Sweden				98	12.0	10.0–14.1
1960	Natvig, Norway	17338	14.5		6345	12.9	

values to be compared and ε the standard error of the difference.

The standard error of the difference is based on the formula

$$= \sqrt{\quad + \varepsilon}$$

in which and ε are the standard errors of the statistics to be compared.

The standard error of the mean values was based on the formula $\varepsilon\bar{X} = \frac{S}{\sqrt{n}}$ in which

= the standard deviation, and

n = the number of observations

The intercorrelation of Hb and SeF HB and TIBC, and of SeF and TIBC was measured by computing the correlation coefficient The deviation of the correlation coefficient from zero was tested with the t test, t = $\frac{}{\varepsilon r}$ in which is the correlation coefficient and εr its standard error

The standard error of the correlation coefficient was obtained from the formula

$$\varepsilon r = \sqrt{\frac{1 - }{n' - 2}}$$

in which = correlation coefficient and

n = number of pairs of observation.

The deviation between the tw methods employed for determination of the serum iron was studied by the t test.

Table 5. Foreign serum iron level (γ %) studies

Year	Authors	Men			Women		
		Number	Mean value	Min.–max.	Number	Mean value	Min.–max.
1937	Heilmeyer & Plotner Germany	25	126	81–162	25	89	64–128
1937	Moore & al., USA	15	122	94–174	15	98	58–14
1939	Skouge Norway	50	118	79–162	50	104	66–164
1940	Brochner Mortensen & Olsen, Denmark	70	132	90–194	20	127	79–191
1940	Sakakura, Japan	20	121	107–135	20	91	70–104
1941	Vahlquist, Sweden	50	142	68–263	50	123	53–210
1942	Bjerre & Christoffersen, Denmark	15	111	72–160	15	103	46–141
1943	Brochner Mortensen, Denmark	50	128	78–194	50	117	79–191
1944	Eckeström, Sweden	50	108	40–196	50	84	30–171
1944	Powell, Great Britain	35	145		35	117	
1944	Segschneider Germany				100	112	44–191
1944	Vahlquist & Neander Sweden	36	118		40	114	
1945	Lövgren, Sweden	17	135		140	105	
1946	Hoyer Denmark	50	131	63–189	50	115	69–197
1946	Waldenström, Sweden				15	113	
1947	Laurell, Sweden	61	124	70–214	59	108	57–196
1948	Cartwright & al., USA	49	105	43– 10	43	104	28–207
1948	Dahl, Sweden				88	109	68–194
1948	Nilsson, Sweden	26	132		21	104	
1949	Cartwright & Wintrobe, USA	15	127	79–196	15	123	101–164
1949	Lundstrom, Sweden				9	127	38–216
1949	Rath & Finch, USA	15	106	81–147	15	94	72–130
1949	Rostrup Denmark	19	120	63–263	24	102	39–210
1950	Andersson, Sweden	20	115	74–189	50	105	61–190
1951	Chaloupka & al., USA				275	116	33–221
1951	Hemmeler France	25	123	118–142	25	109	90–123
1951	Ventura & Klopper Great Britain				25	111	88–131
1952	Davies & al., Great Britain	20	126	76–150	20	104	60–173
1952	Fowler & Barer USA	89	111	20–263	41	92	20–226
1952	Gitlow & Beyers, USA	10	148	74–186			
1952	Pirrie Great Britain	108	109	55–188	98	91	35–143
1953	Brendstrup, Denmark	40	125		40	101	
1953	Hagberg Sweden	26	137		28	123	
1955	Agarwal & Misra, India	50	117	74–220			
1955	Rechenberger Western Germany	86	107		78	101	
1956	Peters et al., USA	43	120	56–183			
1957	Stengle & Schade, USA	10	100	56–206	10	98	43–175
1959	Gupta & al., India	70	123	67–200	30	108	70–133
1959	Verloop & al., Netherlands	20	133	83–180	20	120	82–165

(All mean values in the table are given to the nearest integer)

based on the use of weak hydrochloric acid solution to dialyse the iron from the protein, gives results that are too low since a weak hydrochloric acid solution is unable to liberate all the iron If the analysis is carried out on frozen serum the results, according to Peters et al are particularly low For this reason, the comparison described above between the methods of Schales and Peters et al. was carried out, with determinations in duplicate of 15 sera. No significant difference was found between the results they yielded

The values produced by the methods either slightly too low or too high, are probably of little practical value if iron deficiency is the object of study What Waldenström observed about the morning and evening values probably applies to the methods as well viz. that »values below 40—50 γ ought to be regarded as definitely pathological» for 10—30 per cent errors in such results neither improve nor worsen the results, they are in any case too low On the basis of the approximately 7000 SeFe and TIBC analyses carried out, the greatest sources of error may be given as incomplete centrifuging and careless pipetting of the filtrate. This very easily raises the results but can be avoided if care is taken.

Determination of total iron binding capacity (TIBC)

Methods were selected on the same principles as was that of determining SeFe. Since it was more practical to carry out the entire analysis by the same method, the method described by Peters et al was selected for the determination of TIBC the iron determination which is an integral part of the analysis was also made by the method of Peters et al., which as indicated above gave values identical to those of the Schales method This method of determining TIBC, reported by Peters et al., has only been criticized by Ramsay who found that all physico-chemical methods gave precise results if the associated iron determination method did so According to the critics mentioned the method of iron determination by Peters et al does provide reliable results.

also lower than those quoted by the three Finnish and three Swedish authors mentioned above

The mean values quoted in papers published in other countries are also, almost without exception, lower than those quoted by the Finns mentioned. Heilmeyer & Plötner (1937) quoted a mean value of 126 γ for men and 89 γ % for women Moore et al. (1937) 122 and 98 γ % Cartwright et al. (1948) 105 and 104 γ Rath & Finch (1949) 106 and 94 γ and Davies et al. (1952) 126 and 104 γ % to quote just a few of the best known authors. Serum iron level studies carried out in Scandinavia and most of those undertaken in different parts of the world, principally on selected normal series, are listed in Table 5

3 Total iron binding capacity (TIBC)

No TIBC determinations have as yet been published in Finland, but after Laurell (1947) described his method of determining TIBC, corresponding studies were published in several other countries. They are listed in Table 6.

According to these studies the mean value of TIBC in different series ranges from 253—348 γ % for men and from 250—371 γ % for women, and no statistical difference is noticeable between the sexes. The very different values reported by various authors are attributable to the different methods used. According to Ramsay (1958) values below 250 γ % and above 400 γ are unusual among healthy subjects.

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The values produced by the methods, either slightly too low or too high, are probably of little practical value if iron deficiency is the object of study What Waldenström observed about the morning and evening values probably applies to the methods as well, viz. that values below 40—50 γ ought to be regarded as definitely pathological for 10—30 per cent errors in such results neither improve nor worsen the results they are in any case too low On the basis of the approximately 7000 SeFe and TIBC analyses carried out, the greatest sources of error may be given as incomplete centrifuging and careless pipetting of the filtrate. This very easily raises the results but can be avoided if care is taken

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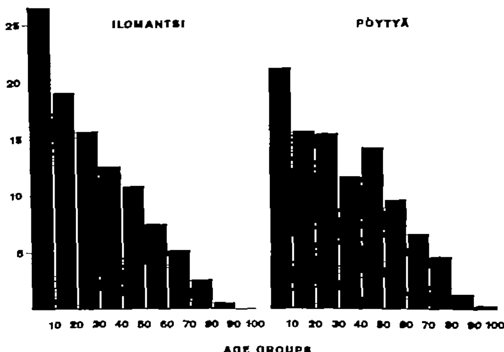


Fig 1 Age distribution of the population of the parishes of Ilomantsi and Pöytyä.

	Ilomantsi	*Pöytyä*
	per cent	
Agriculture and forestry	77.2	65 1
Industry and handicrafts	7 7	17.2
Trade	3 1	3.9
Communications	2.8	3.9
Services	6.2	4 4
No occupation, or occupation unknown	3 0	5.5

The distribution of the population by age groups is shown in Fig 1 The differences between the parishes are greatest in the young age groups 0—19 years and in the old age groups exceeding 70 years.

For the investigation a random sample was taken from among th persons whose ages ranged from 20 to 69 by dividing them into four categories: 20—29 30—39 40—49 and over 50 A group of 65 and for those aged over 50 one of 80 individuals was taken from each category by random figures. The series for each parish therefore totalled 550 persons, 275 men and 275 women.

T bl 8. Mean haemoglobin (g/100 ml) values men and women by ge group

[illegible]	Ilomantsi								Pöytyä							
	Men				Women				Men				Women			
	H lth		Total series		"Healthy		Total series		Healthy		Total series		Healthy"		Total series	
	[illegible]	M Hb and tard r	Number	M Hb and standard error	Number	Mean Hb nd tand rd error	Number	Mean Hb nd standard error	Number	Mean Hb and standard error	Number	Mean Hb and standard error	Number	Mean Hb and standard error	Number	Mean Hb and t ndard error
[illegible]	[illegible]	11) 0 15	58	13 9±0 13	28	12.8±0 02	42	12.7+0.02	8	14.2±0 17	33	14.2±0 16	32	12 6±0 18	51	12.6±0 14
[illegible]	[illegible]	11) 0 21	50	14 1 0 19	11	12 1±0.20	68	12.2 _0.22	46	14 0±0 16	51	14 0 _0 14	47	12.3±0.20	65	12.3±0.17
[illegible]	[illegible]	0 17	58	13 6+0 16	48	12.5±0 16	58	12.5±0 15	51	13 7±0 18	57	13 7±0 17	46	12.0±0.19	57	12 0±0.19
[illegible]	[illegible]	0 1)	53	13 3 0.17	69	12 9±0 13	79	12.9±0 12	50	13 7±0 13	58	13.5±0 14	63	12.6±0.12	70	12.6±0 13
[illegible]	[illegible]	13 0 09	211	13 7 0 08	186	12 6±0 08	215	12.6±0.09	175	13.9±0 08	199	13.8±0 08	188	12.3±0 09	213	12 1±0 08

T ble 9 Mean haemoglobin (g/100 ml) values of healthy men and women, by mar tal status

Marital status	Ilomantsi				Pöytya			
	Men		Women		Men		Women	
	Number	Mean Hb and standard error	Num ber	Mean Hb nd standard error	Number	Mean Hb and standard error	Num ber	Mean Hb and standard error
Married	122	13.7±0.12	157	12.5±0.09	151	13.8±0.09	163	12.3±0.09
Unmarried	54	13 6±0.15	29	13 1±0.19	24	14 1±0.20	25	12.4±0.70
Total	176	13 7±0 09	186	12.6±0.08	175	13 9±0.08	188	12.3±0.09

boarding school) without taking part in hospital work.

It may be said that, prior to the start of the examination, both the conscripts and the student nurses had become accustomed to the tempo of the life they lived throughout the period of the investigation.

The examination was conducted on lines similar to those in Pöytyä and Ilomantsi. It started in December 1960 and the examination to verify the effect of iron treatment was carried out in March 1961.

Methods of investigation

1. Medical history

The following questions concerning medical history data were asked the examinees mainly by the writer in person.

1. Full name
2. Age
3. Occupation
4. Marital status
5. Health during the last year
6. Occasion of the examinee's last more serious infection (not e.g. the common cold)
7. Diagnosis of any malignant tumours
8. Diagnosis of fish tapeworm, and if so, date of expulsion
9. Occurrence of haemorrhages (piles, peptic ulcer etc.) giving dates
10. For the female examinees
    - menstrual periods (scanty, ordinary, profuse, menopause)
    - lapse of time since last delivery
    - number of deliveries in the last 5 years
    - total number of deliveries
11. Iron-containing products which the examinee may have taken during the previous year
12. Time of the examinee's last full meal and food consumed since then
13. Quantity of milk or buttermilk consumed daily
14. Number of days per week when the main meal comprises meat or fish
15. Number of times per week eggs are included in a meal
16. Distance covered to arrive at the place of examination
17. Mode of travel
18. Number of hours examinee slept the previous night
19. Number of hours the examinee had been up before the hour of examination

On the basis of these medical history data, an effort was made to exclude those who in the year preceding the examination had had a disease which directly affects the haemoglobin value or serum iron level of the blood. In this way an attempt was made to eliminate potential errors arising from anaemia, severe infection, malignant tumour and persistent haemorrhage. Pregnant and lactating mothers, and those who for one reason or another had taken iron products were excluded from the »healthy» group. For the sake of comparison, it was found useful in the tables giving the results of the first examination to include both the total series and the »healthy» subjects, but this was not necessary in the review of the results. No clinical examination was performed.

Since the examinations were often carried out in difficult circumstances and those invited lived up to a distance of about 40 miles from the place of examination, the principle of having everybody attend the examination in the morning had to be abandoned. In Ilomantsi, in particular, where a number of those examined were forest workers who left for work at 0500 in the morning, it would have been completely impossible. The test subjects were divided into two groups, and one was examined between 0800 and 1200 hours, the other between 1500 and 1800 hours, though even these hours could not be rigorously imposed.

2. Determination of haemoglobin

The haemoglobin was determined by the cyanmethaemoglobin method described by Crosby et al. (1954). A Ljungberg photometer was employed for the measurement.[1] The standards used for the measurement were Hemotrol (Clinton Laboratories, Los Angeles) and Acuglobin (Ortho Pharmaceutical Corporation, Raritan) standards intended for cyanmethaemoglobin determination.

The specimens were drawn from the finger tip in the usual way by a 0.02 ml calibrated pipette. The 0.02 ml specimen was immediately placed in 5 ml of Drabkin's (1935) solution already measured into the test tube; the solution contained, per litre of distilled water, 1 gram $NaHCO_3$, 52 mg KCN and 198 mg $K_3Fe(CN)_6$. The pipette was carefully rinsed in the solution in order that the whole blood specimen should be included in the solution. Measurement by photometer was taken at the

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[1]) The photometer was calibrated by Mr. Y. Rantanen, M. Sc., of the Institute of Occupational Health.

PER CENT

50
40
30
20
10

PÖYTYÄ:
MEN

TOTAL SERIES
(199)

„HEALTHY"
(175)

2 12 24 73 59 28 1

8 9 10 [1] 11 12 13 14 15 16 [1] 17 Hb g/100 ml

Fig. 3 a. Distribution of the haemoglobin values of Pöytyä men

PER CENT

50
40
30
20
10

PÖYTYÄ:
WOMEN

TOTAL SERIES
(243)

„HEALTHY"
(188)

1 1 7 25 56 80 62 8 3

[1] 8 9 [4] 10 11 12 13 14 15 [3] 16 17 Hb g/100 ml

Fig. 3 b. Distribution of the haemoglobin values of Pöytyä women

For determination of TIBC the course of the analysis continued as follows

- 1 drop of concentrated hydrochloric acid and 1 drop of thioglycolic acid are added to 5 ml of supernatant obtained after the elimination of resin. The solution is mixed by swirling and left for 30 min. t room temperature.
- 1 ml of 30 trichloracetic acid is added, the solution is mixed with stirring rod and left for 15—30 min. at room tempera ure covered by paraffin film.
- Centrifuged for about 15 min. t rate of 2000 RPM.
- 4 ml of the supernatant is pipetted.
- 0.5 ml of saturated sodium acetate solution and 2 ml of alcoholic bathophenanthroline solution are added, and mixed by swirling.
- Measured at wavelength 535 μm (Beckman DU) after some 10—15 min when the red colour is fully developed, using 2 ml of redistilled wa er as blank alue

Known iron solutions were employed as standard for the determination of both serum iron and TIBC. They were prepared daily from stock solution containing 1 mg of iron per 1 ml water For serum iron determinations the standards for each series, in duplicate, were solutions containing 50 100 and 200 γ % /2 ml and for TIBC determination, those containing 100, 200 and 400 γ %/1 ml, respectively The values against extinction readings were read off from the line given by these know solutions.

All determinations, with few exceptions, were carried out in duplicate, in series of 24 analyses. If there was not enough serum for determination in duplicate, it was diluted by one-half of iron-free redistilled water and the corresponding correction was taken into account in the results. T ensure that the iron values given by the Schales method and that of Peters et al. were of the same magnitude comparative iron determination was performed of identical sera by both methods, and the results obtained were

	Schales	*Peters et al.*
Serum I	99	97
II	95	97
III	68	65
IV	71	68
V	55	60
VI	68	68
VII	43	41
VIII	86	90
IX	94	90
X	120	124
XI	76	73
XII	106	102
XIII	82	80
XIV	68	65
XV	132	130
Mean value	84.2 γ /	83.5 γ /

No statistically significant difference ($p = 0.076$) was noticeable between th two methods.

I connection with the first examination, every alternate examinee was given 100 iron tablets and the other 100 placebo tablets, in the order i which they presented themselves for the examination. The iron blets contained 0.2 g f ferrous gluconate, an amount equal to 22 mg of ferrous iron. The placebo tablets contained 0.. g of lactic calcium. The tablets were produced for the occasion by Pharmaceutical Manufacturers Orion Oy using the press-coating method. Both tablets were similar in size, shape and colour and their packings were identical. Those examined were asked to tak these tablets during the month following examination, 1 tablet 3 times daily before meals. At the follow-up examination the subjects were asked how many tablets they had taken.

5. Statistical treatment

T establish statistically the hange between the first and second measurements, the mean value ($\bar{X}$) of the intra-individual change between first and second measurements and its standard error ($\bar{X}$) were calculated for the iron and the placebo groups.

These alues were employed to test

(1) whether statistically significant change had taken place in the groups from one measurement to the next, in other words, whether $\bar{X}$ was significantly above or below zero.

(2) whether the change was greater in the iron group than in the placebo group.

T throw light on question (2) the difference between the average changes of the groups and its standard error were calculated. The deviation of group averages from zero or the difference between group averages was considered not significant if the probability that the result was due to chance was 5 per cent or more.

The classes of significance employed for the results were

not significant if probability of risk is	$P \geq 0.05$
almost significant if probability of risk is	$0.05 > P \geq 0.01$
significant if probability of risk is	$0.01 > P \geq 0.001$
highly significant if probability of risk is	$0.001 > P$

The following formulae were applied to calculate and test the statistics (Ahmavi—Pöyhönen 1954)

Comparison of two mean values (t test) t = $\frac{\bar{X}_1 - \bar{X}_2}{}$ in which $\bar{X}_1$ and $\bar{X}_2$ are the mean

PER CENT

50
40
30
20
10

PÖYTYÄ
MEN

TOTAL SERIES
(199)

„HEALTHY"
(175)

2 12 24 73 60 28 1

1 1

8 9 10 11 12 13 14 15 16 17 Hb g/100 ml

Fig. 3 a Distribution of the haemoglobin values of Pöytyä men.

PER CENT

50
40
30
20
10

PÖYTYÄ:
WOMEN

TOTAL SERIES
(243)

„HEALTHY"
(188)

1 1 7 25 56 80 62 8 3

1 4 3

8 9 10 11 12 13 14 15 16 17 Hb g/100 ml

Fig. [illegible] Distribution of the haemoglobin values of Pöytyä women.

DISCUSSION OF THE METHODS EMPLOYED

Determination of haemoglobin (Hb)

In 1954 the National Academy of Sciences and the National Research Council in the USA appointed a committee to study the standardization of haemoglobin determinations. The work of this committee was described by Cannan in 1958 in several leading medical science periodicals. The committee recommended as the standard method the cyanmethaemoglobin method reported by Crosby et al. (1954). The WHO »Study Group on Iron Deficiency Anemias» also decided in 1959 to recommend the cyanmethaemoglobin method as the standard method in anaemia studies.

One of the advantages of this method is the fact that cyanmethaemoglobin keeps well in sterile conditions, thus facilitating the preparation of standards suitable for determinations. All forms of haemoglobin other than sulfhaemoglobin are covered by the determination. The light absorption band of cyanmethaemoglobin is broad and relatively flat, and the errors are consequently smaller. The reagent keeps well and the amount of standard employed is so small that no risk of poisoning exists.

Since the photometer used was duly standardized and the commercial standards applied met the requirements of the cyanmethaemoglobin method, it may be assumed that the methods employed in the determination of haemoglobin meet international requirements and may be considered reliable.

Determination of serum iron (SeFe)

Of the various methods which existed for determining the serum iron level, a method was sought which would be suitable for studying serum specimens taken in field conditions. Since it would not be possible to insist that patients fasted before the examination, it was necessary to choose a method in which the lipids are precipitated and so eliminated. In field conditions it is more difficult to obtain completely non-haemolysed sera by centrifuging, and this was a second fact to be borne in mind. The Schales method was therefore selected, since it seemed to be suitable for these conditions.

The method is a fairly new modification, and no criticism of the method has been traced in literature. The methods of Heilmeyer & Plötner and of Barkan & Walker on which the Schales method is based, have, however been severely criticized (Hemmeler 1951, Peters et al 1956, and Ramsay 1958). Criticism has usually been levelled at the fact that the method,

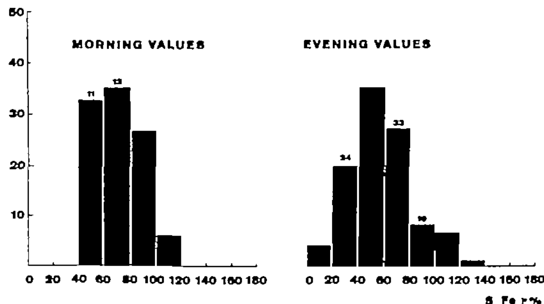


Fig 5. Distribution of the serum iron values of the »healthy» men of Ilomantsi.

PER CENT
50
40
30
20
10
MORNING VALUES
EVENING VALUES
0 20 40 60 80 100 120 140 160 180
0 20 40 60 80 100 120 140 160 180
SeFe γ%

Fig 6 Distribution of th ser m lues of the »healthy women of Ilomantsi

RESULTS

First examination

1 Haemoglobin (Hb)

(a) Ilomantsi

In Ilomantsi the haemoglobin of 219 men and 245 women wa examined they included 176 »healthy» men and 186 healthy» women (Table 7 Fig 2) The arithmetic mean haemoglob n of the healthy» men was 13 7 g/100 ml (range 9.9—16.9 g/100 ml) and of the women 12 6 g/100 ml (range 9 0—15.9 g/100 ml) Taking the WHO Study Group proposed limits, 14 0 g/100 ml for men and 12.0 g/100 ml for women as the Hb values below which anaemia can be considered to exist, 98 men (55 7 per cent) and 45 women (24.2 per cent) came in this category

By age groups (T ble 8) the values are so divided that the highest mean value for men, 14 0 g/100 ml, was recorded for those aged 30—39 and the lowest, 13.2 g/100 ml, for those over 50 This difference between the groups was significant ($p < 0.01$) The difference between the mean value for those aged 20—29 (13.9 g/100 ml) and that of the group over 50 was also significant ($p < 0.01$) For women, the group over 50 showed the highest mean value 12.9 g/100 ml while those aged 30—39 showed the lowest 12.1 g/100 ml. This difference was significant ($p < 0.001$)

A comparison of the difference between the married and unmarried men and women revealed that there was no significant difference in the mean value of the haemoglobin of the men (Table 9 p 0 05) while the mean value of unmarried women, 13 1 g/100 ml, was higher than that of married women, 12.5 g/100 ml. This difference is significant ($p < 0.05$)

When the results are considered according to the occupation of the persons examined (Table 10) it is found that the highest mean value 14.2 g/100 ml was recorded for men employed in light manual work, and the lowest, 13.5 g/100 ml, for forest workers. The difference between the groups is significant ($p < 0.01$) Similarly for women the group of light manual workers showed the highest mean value, 12.9 g/100 ml, and those engaged in intellectual work the lowest 12.2 g/100 ml. The difference between these groups, however was not significant ($p > 0.05$)

(b) Pöytyä

The haemoglobin of 199 men and 243 women was examined 175 men and 188 women were »healthy» (Table 7 and Fig 3)

Table 15. Mean SeF (γ) values of "healthy" men and women, by type of occupation

Type of occupation	Homantsi								Pöytyä							
	Men				Women				Men				Women			
	Morning		Evening		Morning		Evening		Morning		Evening		Morning		Evening	
	Number	Mean SeFe and standard error	Number	Mean SeFe and standard error	Number	Mean SeFe and standard error	Number	Mean SeFe and standard error	Number	Mean SeFe and standard error	Number	Mean SeFe and standard error	Number	Mean SeFe and standard error	Number	Mean SeFe and standard error
Heavy manual work	72	72 ± 4.23	26	55 ± 5.53	116	67 ± 2.33	21	58 ± 4.66	77	63 ± 2.96	59	49 ± 2.87	81	42 ± 2.74	62	32 ± 2.17
Light manual work	7	66 ± 3.96	19	55 ± 5.00	15	67 ± 4.70	12	53 ± 4.35	6	57 ± 11.97	20	31 ± 6.19	6	65 ± 9.59	16	37 ± 4.37
Intellectual work	4	79 ± 14.18	5	80 ± 13.00	8	64 ± 1 .02	5	68 ± 6.88	3	70 ± 11.93	7	39 ± 7.63	5	60 ± 12.55	7	52 ± 2.91
Forest work	1	44	73	58 ± 2.51												
Total	34	72 ± 3.50	123	58 ± 2.12	139	68 ± 2.11	38	58 ± 3.08	86	66 ± 2.80	86	49 ± 2.51	95	45 ± 2.64	85	35 ± 1.60

PER CENT

50
40
30
20
10

ILOMANTSI:
MEN

TOTAL SERIES
(219)

„HEALTHY"
(178)

72
61
37
26
16
1
3
3

8 9 10 11 12 13 14 15 16 17 Hb g/100 ml

Fig 2 a Distribution of the haemoglobin values of Ilomantsi men.

PER CENT

50
40
30
20
10

ILOMANTSI:
WOMEN

TOTAL SERIES
(245)

„HEALTHY"
(186)

84
78
45
16
17
4
1
3

8 9 10 11 12 13 14 15 16 17 Hb g/100 ml

Fig 2 b Distribution of the haemoglobin values of Ilomantsi women.

Table 16. Distribution of SeF values among men and women in Pihtipd

SeF)	Men								Women							
	Morning				Evening				Morning				Evening			
	"Healthy"		Total series		"Healthy"		Total series		"Healthy"		Total series		"Healthy"		Total series	
	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent
0–19	2	2.30	2		8	9.30	10	10.20	14	14.70	16	13.40	19	22.30	26	23.00
20–39	13	15.10	16	16.30	7	31.10	30	30.60	31	32.70	36	30.30	33	38.80	45	39.80
40–59	29	33.0	33	33.70	29	33.70	32	32.0	25	26.30	31	26.10	26	30.60	32	28.30
60–79	19	22.10	21	21.40	13	15.10	16	16.30	15	15.80	21	17.60	6	7.10	9	8.00
80–99	15	17.40	17	17.10	7	8.20	8	8.20	7	7.40	12	10.10	1	1.20	1	0.90
100–119	5	5.80	5	5.10	2	2.30	2	2.00	2	2.10	2	1.70				
120–139	3	3.50	4	4.10												
140–159									1	1.00	1	0.80				
Total	86	100	98	100	86	100	98	100	95	100	119	100	85	100	113	100

Table 17. Mean SeFe (γ) values in Pihtipd, by age group

Age groups	Men								Women							
	"Healthy"				Total series				"Healthy"				Total series			
	Morning		Evening		Morning		Evening		Morning		Evening		Morning		Evening	
	Number	Mean SeF and standard error	Number	Mean SeF and standard error	Number	Mean SeF and standard error	Number	Mean SeF and standard error	Number	Mean SeF and standard error	Number	Mean SeFe and standard error	Number	Mean SeFe and standard error	Number	Mean SeFe and standard error
20–29	14	82 ± 8.97	14	31 ± 7.52	15	83 ± 8.40	18	55 ± 6.29	14	52 ± 6.90	17	46 ± 5.09	20	53 ± 5.98	28	42 ± 3.74
30–39	20	68 ± 5.07	25	46 ± 4.60	22	67 ± 4.76	28	45 ± 4.48	22	48 ± 6.35	5	35 ± 2.95	27	51 ± 5.67	38	36 ± 2.59
40–49	23	59 ± 4.73	27	18 ± 1.74	27	61 ± 5.34	29	48 ± 4.44	20	31 ± 3.70	23	29 ± 3.32	27	36 ± 3.34	27	26 ± 3.09
50 and more	29	54 ± 3.92	20	49 ± 3.45	34	51 ± 3.66	23	47 ± 3.85	39	15 ± 4.25	20	30 ± 3.39	45	16 ± 3.85	20	30 ± 3.39
Total	86	66 ± 2.80	86	49 ± 2.51	98	[illegible]	8	49 ± .34	95	15 ± 2.61	85	35 ± 1.60	119	17 ± 2.36	113	34 ± 1.66

Table 10 Mean haemoglobin (g/100 ml) values of »healthy» men and women, by type of occupation

Type of occupation	Ilomantsi				Pöytyä			
	Men		Women		Men		Women	
	Number	Mean Hb and standard error	Number	Mean Hb and standard error	Number	Mean Hb and standard error	Number	Mean Hb and standard error
Heavy manual work	49	13.7±0.19	144	12.6±0.10	139	13.8±0.10	15[illegible]	12.2±0.10
Light manual work	30	14.2±0.21	29	12.9±0.15	26	14.2±0.17	22	12.8±0.23
Intellectual work	11	13.7±0.36	13	12.2±0.36	10	13.9±0.24	14	13.0±0.28
Forest work	86	13.5±0.13						
Total	176	13.7±0.09	186	12.6±0.08	175	13.9±0.08	188	12.5±0.09

The arithmetic mean haemoglobin of the »healthy» men was 13.9 g/100 ml (range 10.4–16.2 g/100 ml) that of »healthy» women 12.4 g/100 ml (range 7.9–15.5 g/100 ml). Values under 14.0 g/100 ml were recorded for 96 men, i.e. 54.9 per cent, and values under 12.0 g/100 ml for 59 women, i.e. 31.3 per cent.

The distribution of values by age groups (Table 8) showed that the highest mean value for men 14.2 g/100 ml was recorded for the age group of 20–29 years, while the lowest, 13.7 and 13.7 g/100 ml were *recorded for groups of 40–49 and over 50.* The differences between these groups were significant ($p < 0.05$). For women the highest mean value 12.6 g/100 ml was shown by the 20–29 age group and by those over 50 while the lowest, 12.0 g/100 ml was recorded for the group 40–49 years. The difference between the groups of 40–49 years and over 50 years was significant ($p < 0.01$). The difference between the groups 40–49 and 20–29 years was also significant ($p < 0.05$).

A comparison of the mean haemoglobin values of the married and unmarried (Table 9) showed that unmarried men had a slightly higher mean value, 14.1 g/100 ml, than the married, whose mean value was 13.8 g/100 ml. This difference, however was not significant ($p > 0.05$) nor was there any significant difference between the married and the unmarried women ($p > 0.05$).

Classification according to occupation (Table 10) showed that men engaged in light manual work had the highest mean value *14.2 g/100 ml, and those in heavy* manual work the lowest, 13.8 g/100 ml. The difference between these groups was significant ($p < 0.05$). For women, the group engaged in intellectual work had the highest mean value, 13.0 g/100 ml and that doing heavy manual work had the lowest, 12.2 g/100 ml. This difference was significant ($p < 0.01$). The difference between the groups engaged in heavy manual work and light manual work was also significant ($p < 0.05$).

doing light manual work, 37 γ %, was significantly lower ($p < 0.01$) than that of the group of intellectual workers, 52 γ %.

(c) National servicemen

A total of 53 national servicemen attended the examination. The arithmetic mean of SeFe was 98 γ % (range 36–178 γ %). All the specimens were taken in the morning. 15 of the examined i.e. 28.3 per cent, gave a result below 80 γ %. The distribution of results is shown in Table 18 and Fig. 9.

(d) Student nurses

The investigation comprised 44 student nurses for whom the arithmetic mean was 93 γ % (range 46–149 γ %). All specimens were taken in the morning. Only 3 of the examined 6.8 per cent, showed an SeFe value below 60 γ %. The distribution of the results is given in Table 18 and Fig. 9.

Table 18. Distribution of the SeFe values for national servicemen and student nurses

SeFe γ %	National servicemen		Student nurses	
	Number	Per cent	Number	Per cent
20–39	1	1.90		
40–59	7	13.20	3	6.80
60–79	7	13.20	8	18.20
80–99	18	34.00	17	38.60
100–119	7	13.20	8	18.20
120–139	3	5.70	7	15.90
140–159	6	11.30	1	2.30
160–and more	4	7.50		
Total	53	100.00	44	100.00

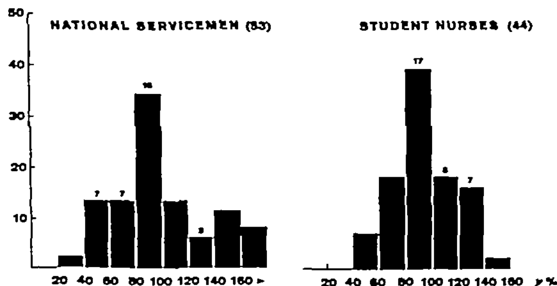


Fig. 9. Distribution of the serum iron values of national servicemen and student nurses.

(c) National servicemen

The haemoglobin of 53 healthy national servicemen was examined The distribution of the results is shown in Table 11 and Fig 4 The arithmetic mean haemoglobin was 14.2 g/100 ml (range 11.8–16.1 g/100 ml) Eighteen, or 33.9 per cent, had a haemoglobin value below 14 0 g/100 ml

(d) Student nurses

The results of an examination of the haemoglobin of 44 healthy student nurses are given in Table 11 and Fig 4 The arithmetic mean haemoglobin was 12.9 g/100 ml (range 11 1–14 6 g/100 ml) Six of the nurses, or 13 6 per cent, had a haemoglobin value below 12.0 g/100 ml.

Table 11 Distribution of the haemoglobin values for national servicemen and student nurses

Hb g/100 ml	National servicemen		Student nurses	
	Number	Per cent	Number	Per cent
11 0–11.9	1	1.90	6	13.60
12.0–12.9	5	9 40	19	43.20
13.0–13.9	12	22.60	13	29.60
14 0–14.9	23	43.40	6	13.60
15 0–15.9	10	18.90		
16 0–16.9	2	3.80		
Total	53	100.00	44	100.00

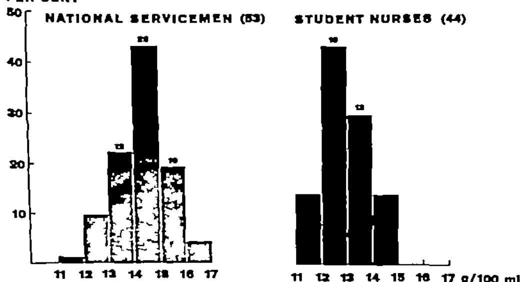


Fig 4 Distribution of the haemoglobin values of national servicemen and student nurses.

Table 20 Mean TIBC (γ %) values in Ilomantsi by age group

Age groups	Men				Women			
	"Healthy"		Total series		"Healthy"		Total series	
	Number	Mean TIBC and standard error	Number	Mean TIBC and standard error	Number	Mean TIBC and standard error	Number	Mean TIBC and standard error
20–29	37	335±5.08	50	337±4 75	20	333±7.07	32	337±5.61
30–39	35	348±5.67	42	347±4.97	36	354±8.18	59	351±5.88
40–49	45	344±5 40	52	346±4.96	41	343±7 04	50	341±6.19
50 and more	37	347±6.03	47	348±6 19	57	345±4 49	63	347±4 47
Total	154	344± 79	191	344±2.49	154	345±3.29	204	345±2.80

Table 21 Distribution of the TIBC values for men and women in Pöytyä

TIBC γ %	Men				Women			
	"Healthy"		Total series		"Healthy"		Total series	
	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent
200–249			1	0.50	1	0 60	4	1.90
250–299	33	20 10	34	18.90	37	22.00	47	22.00
300–349	65	39 70	73	40 60	48	28.60	55	25 70
350–399	44	26.80	47	26.10	39	23.20	54	25.20
400–449	19	11.60	22	12.20	32	19.00	43	20 10
450–499	3	1.80	3	1 70	11	6 60	11	5.10
Total	164	100.00	180	100.00	168	100 00	214	100 00

Table [illegible] Mean TIBC (γ %) values in Pöytyä, by age group

Age groups	Men				Women			
	"Healthy"		Total series		"Healthy"		Total series	
	Number	Mean TIBC and standard error	Number	Mean TIBC and standard error	Number	Mean TIBC and standard error	Number	Mean TIBC and standard error
20–29	28	334 10 5	37	335 9.56	28	327±10.34	43	333± 8.20
30–39	44	330 6 68	48	330 6 17	44	354± 9 43	59	351± 7 [illegible]
40–49	48	355 7.23	51	35[illegible] 7 [illegible]7	41	379 8.41	51	376± 7.80
50 and more	44	34[illegible] 6 87	49	344 6. [illegible]8	55	346 7.97	61	34[illegible] 8.15
Total	164	341 3.83	180	341 3 [illegible]7	168	333 4 63	214	352± 4 15

SeF γ%	Morning				Evening				Morning				Evening			
	"Healthy"		Total series		"Healthy"		Total series		"Healthy"		Total series		"Healthy		Total series	
	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent
0–19					4	3.20	5	3.30								
20–39			1	2.20	24	19.50	30	19.90	19	13 70	21	11.80	4	10.50	8	14 00
40–59	11	32.30	13	28.90	43	35.00	54	35.80	40	28.80	55	30.90	20	52 60	24	42.10
60–79	12	35.30	15	33.30	33	26.80	40	26.50	42	30.20	48	27 00	8	21 10	13	22.80
80–99	9	26.50	11	21.50	10	8.10	12	7.90	21	15 10	35	19 70	4	10.50	10	17 60
100–119	2	5.90	4	8.9	8	6.50	9	5.90	14	10.10	16	9 00	2	5.30	2	3.50
120–139					1	0.90	1	0.70	2	1 40	2	1 10				
140–159									1	0.70	1	0.50				
Total	34	100	44	100	123	100	151	100	139	100	178	100	38	100	57	100

Table 13. Mean SeF (γ) values in Ilomentsi, by ge group

Age groups	Men								Women							
	"Healthy				Total series				"Healthy				Total series			
	Morning		Evening		Morning		E ening		Morning		Evening		Morning		E ening	
	Number	Mean SeFe and standard error	Number	Mean SeFe and standard error	Number	Mean SeFe and standard error	Number	Mean SeFe and standard error	Number	Mean SeFe and standard error	Number	Mean SeFe and standard error	Number	Mean SeFe and standard error	Number	Mean SeF and standard error
20–29	1	82	37	60±4.01	3	120±25.36	48	60±3.54	21	77±4.09	7	57±2.77	30	77±3.39	12	61±1.57
30–39	5	60±7.31	31	53±4.03	8	71± 7 49	33	55±3.81	30	65±5.35	10	66±7.58	46	61±3.92	21	64±4.99
40–49	12	79±6.41	34	57±3.75	12	79± 6.41	41	56±3.34	35	71±4 77	11	59±6.09	44	71±1.05	12	61±6.72
50 and more	16	67±4.21	21	60±5.98	22	63± 3.58	27	57±4.94	53	60±2.68	10	49±3.29	38	62±2.77	12	49±2.92
Total	34	72±3.50	123	58±2.12	45	72± 3.70	151	58±1.90	139	68±2.11	38	58±3.08	178	68±1.51	57	59±2.62

(c) National servicemen

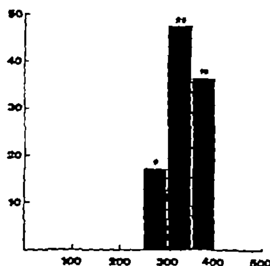
The TIBC of 53 national servicemen was tested. Results are given in Table 23 and Fig 12 and the arithmetic mean value obtained was 336 γ (range 257 —393 γ %) 35.8 per cent had values above 350 γ %.

(d) Student nurses

The TIBC of 44 student nurses was tested, and their arithmetic mean was found to be 323 γ % (range 243—419 γ %) The distribution of the values can be seen from Table 23 and Fig 12 22.7 per cent had values above 350 γ %.

Table 23 Distribution of the TIBC values for national servicemen and student nurses

TIBC γ %	National servicemen		Student nurses	
	Number	Per cent	Number	Per cent
200—249			1	2.30
250—299	9	17.00	12	27.30
300—349	25	47.20	21	47.70
350—399	19	35.80	9	20.40
400—and more			1	2.30
Total	53	100.00	44	100.00



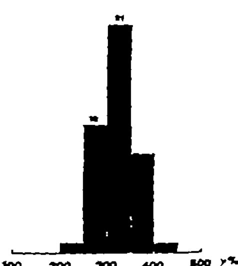


Fig 12 Distribution of the values of the total iron binding capacity of national servicemen and student nurses.

Table 11 Mean SeF (γ %) values of healthy men and women by marital status

Marital status	Homantsi								Pövya							
	Men				Women				Men				Women			
	Morning		Evening		Morning		Evening		Morning		Evening		Morning		Evening	
	Number	Mean SeF and standard error	Number	Mean SeF and standard error	Number	Mean SeF and standard error	Number	Mean SeF and standard error	Number	Mean SeF and standard error	Number	Mean SeF and standard error	Number	Mean SeF and standard error	Number	Mean SeF and standard error
Married	32	71 ± 3.50	74	60 ± 2.78	120	67 ± 2.32	31	59 ± 3.74	76	62 ± 2.81	72	46 ± 2.62	06	44 ± 2.78	69	31 ± 1.54
Unmarried	2	59 9.00	49	55 ± 3.51	19	69 ± 5.0?	7	55 ± 2.14	10	70 ± 11.05	14	61 ± 6.68	9	13 ± 8.86	16	49 ± 4.72
Total	34	72 ± 3.50	123	58 ± 2.12	139	68 ± 2.11	38	58 ± 3.08	86	66 ± 2.80	86	49 ± 2.51	95	15 ± 2.64	85	35 ± 1.60

5 Hb and SeFe values by family

An attempt was made to clarify the possible incidence of iron deficiency by family in that Table 25 gives the mean Hb and SeFe values for men whose wives or sisters living in the same household showed an Hb value above or below 12.0 g/100 ml or an SeFe value above or below 60 γ. *It was found that the mean* haemoglobin values of men living in the same household with women whose Hb value was below 12.0 g/100 ml did not differ significantly ($p > 0.05$) from those of men living in the same household with women whose Hb value was over 12.0 g/100 ml. Nor was any significant ($p > 0.05$) difference noted between the mean SeFe values of men in the same household as women showing SeFe values above or below 60 γ.

Table 25. Hb and SeFe values for the male family members when "healthy" women showed Hb values ≤ 12.0 g/100 ml and SeF (morning) values ≤ 60 γ.

Parish	Women's Hb				Women SeF (morning values)			
	< 12.0		> 12.0		< 60.0		> 60.0	
	Number	Mean value for men	Number	Mean value for men	Number	Mean value for men	Number	Mean value for men
Ilomantsi	10	13.4	51	13.9	5	62.0	17	74.0
Pöytyä	57	13.8	103	13.9	35	62.0	13	66.0

6 Correlations between haemoglobin and serum iron and between serum iron and total iron binding capacity

These correlations are shown in Table 26.

A positive significant correlation between haemoglobin and the morning values of serum iron was noted in Ilomantsi for women but not for men. In Pöytyä the correlation was significant for both men and women. Among the national servicemen and the student nurses the correlation was not significant. In Ilomantsi and Pöytyä the correlation between the evening values of haemoglobin and serum iron was also calculated but was not significant in any of the groups.

The correlation between serum iron and the total iron binding capacity was significantly positive in Ilomantsi and Pöytyä. No difference on this point was noted between the morning and evening values of serum iron. For the national servicemen and student nurses no significant correlation between these values was shown.

values of the two groups engaged in manual work were of the same magnitude without significant difference ($p > 0.05$)

(b) Pöytyä

The serum specimen required for the investigation was obtained from 196 men, of whom 172 were »healthy» and from 232 women, of whom 180 were »healthy» The results are shown in Table 16 and Figs. 7 and 8. Of the 172 men, 86 came for the examination in the morning Their SeFe mean value was 66 γ (range 18 –128 γ) For the other 86 examined in the afternoon the mean value was 49 γ % (range 6–110 γ %) Of the 180 women, 95 were examined in the morning and gave a mean value of 45 γ % (range 5–156 γ %) 85 were examined in the afternoon, with a mean value of 35 γ (range 5–84 γ %)

If the previously mentioned lower limits of the values in clinical use are applied, 73.2 per cent of the morning values and 89.5 per cent of the evening values for the men were below this limit (80 γ /) For the women, 73 7 per cent of morning and 91 7 per cent of evening values failed to reach this limit (60 γ %)

The distribution of the results by age group (Tabl 17) shows the highest mean value for men n the 20–29 age group 82 γ % for morning values and 54 γ % for evening values. The lowest mean of morning values, 54 γ was recorded for the group over 50 and the lowest mean of evening values, 46 γ for th 30–39 age group.

The differences were significant between the groups of 20–29 and over 50 years ($p < 0.01$) of 20–29 and 30–39 years, 30–39 and over 50 years ($p < 0.05$)

For women, too, the 20–29 age group showed the highest mean values 52 γ % in the morning and 46 γ % in the afternoon. The lowest means were recorded for the 40–49 age group: 34 γ in the morning and 29 γ in the evening These differences in morning values were significant between the groups of 20–29 and 40–49 years ($p < 0.05$) and in evening values between the groups of 20–29 and both 40–49 and over 50 years ($p < 0.01$)

The mean values for married men were lower both in the morning and in the evening than those for the unmarried (Table 14) The mean morning value for the married was 62 γ % and mean evening value 46 γ % while the figures for the unmarried were 70 γ % and 61 γ %, respectively The difference is significant for evening values only ($p < 0.05$) no significant difference existed between morning values ($p > 0.05$)

The morning values for women showed no significant difference ($p > 0.05$) while the mean evening valu for the unmarried, 49 γ % was significantly higher ($p < 0.001$) than that for the married, 31 γ %

A comparison of SeFe mean values according to the type of occupation (Table 15) showed no significant difference ($p > 0.05$) for the groups engaged in manual work.

The mean morning valu for women employed on *heavy manual work, 42 γ %* was significantly lower ($p < 0.01$) than that for the group on light manual work, 65 γ %. The difference in evening values was also significant ($p < 0.001$) between th mean for those engaged in heavy manual work, 32 γ % and that for women doing intellectual work, 52 γ %. The mean evening value of the group

on mean and standard deviation in first and second examinations and the significance of the changes in these mean values

Iron group						Placebo group						Significance of changes		
First examination			Second examination			First examination			Second examination					
Number	Mean value	Standard deviation	Number	Mean value	Standard deviation	Number	Mean value	Standard deviation	Number	Mean value	Standard deviation	Iron group	Placebo group	Difference between changes
7	71	20.07	7	68			72	18.12	21	66	28.59	> 0.05	> 0.05	> 0.05
52	68	23.91					67	26.14	56	66	31.88	> 0.05	> 0.05	> 0.05
59	(					)	68	24.22	77	66	31.06	> 0.05	> 0.05	> 0.05
					21 78	38	63	26.71	38	66	76.33	> 0.05	> 0.05	> 0.05
			34	61	96.25	48	46	26.13	48	56	29.34	0.001	0.05	> 0.05
		.83	73	67	21 02		3	27.56	86	60	20.31	0.01	0.05	0 05
		3 71						8	59	66	27.25	0.05	> 0.05	> 0.05
							57	28.13	104	61	30 98	0.001	0.05	0.05
						163	60	27 07	163	63	29.68	0.05	> 0.05	0 05
					25 08	29	99	1.95	28	98	28.38	< 0.05	> 0.05	0.05
				113	30.38	23	93	31 7	23	89	31 17	0.01	0.05	< 0.01

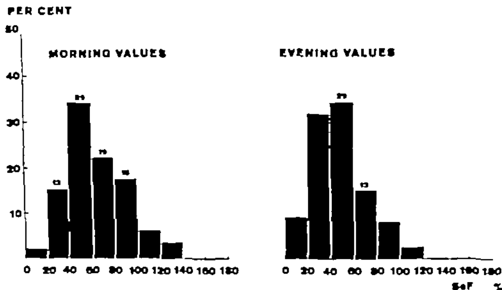


Fig 7 Distribution of the serum iron values of the »healthy» men of Pöytyä.

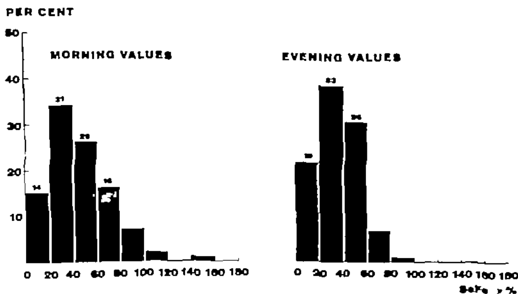


Fig 8 Distribution of th serum iron values of the »healthy» women of Pöytyä.

DISCUSSION

The sampling method for the series studied was such that conclusions may be drawn for the entire population of the parishes. Although for much of the material conclusions were drawn only for the »healthy» subjects, this was done with the knowledge that this »healthy» section is compatible with the total series, for the mean values of the »healthy» groups and those of the total series do not differ significantly. In order to demonstrate this, both series were listed side by side in Tables 7 8 12 13 16 17 19 20 21 and 22. The investigation, however was also concerned with the extent to which the haemoglobin, serum iron and total iron binding capacity of the »healthy» people examined differed from the normal values routinely applied in clinical work.

The second part of the series, the national servicemen and student nurses, was selected. Th examinat on f these subjects w ma nl ntended t discover whether ther w differen between the selected ma series ... selected ser es At th ... he q ... eq red wa ... as th s was done ... w ll be ... sed later.

The mean Hb value was 13 7 g/100 ml for Ilomantsi men, 13 ... g/100 ml for Pöytyä the mean morning value of serum iron 72 γ in Ilomantsi was 66 γ in Pöytyä. The mean TIBC was 344 in Ilomantsi and 341 γ in Pöytyä. The difference between these mean values is not significant ($p > 0.05$)

A comparison by age group of the mean values obtained revealed a significant difference ($p < 0.05$) in mean Hb values of men over 50 years of age in Ilomantsi (13.2 g/100 ml) and in Pöytyä (13 7 g/100 ml) In mean SeFe values a significant difference ($p < 0.05$) between the men of these parishes was noted only in the group of men aged 40–49 (Ilomantsi 67 γ and Pöytyä 54 γ) The TIBC mean values also differed significantly ($p < 0.05$) in only one age group, that of men aged 30–39 (Ilomantsi 318 γ and Pöytyä 330 γ)

A comparison of the men of Ilomantsi and Pöytyä according to type of occupation revealed no significant difference (p ... 0.0 ...) in Hb values. For SeFe mean values the evening values must be compared because the morning value groups remained too small. It was found that only intellectual workers in Ilomantsi showed a significantly higher ($p < 0.01$)

3. Iron binding capacity of the serum (TIBC)

(a) Ilomantsi

A serum specimen sufficient for the TIBC test was obtained in Ilomantsi from 191 men, of whom 154 were »healthy» and from 201 women of whom 154 were »healthy» The results are given in Table 19 and Fig 10 The arithmetic mean value for the »healthy» men was 344 γ % (range 274—432 γ) and that for the »healthy» women 345 γ % (range 250—460 γ %) The distribution of values is shown in Table 19 38.5 per cent of men and 44.2 per cent of women had values above 350 γ %.

No significant difference ($p > 0.05$) was visible between men of different age groups (Table 20) Among the women the mean TIBC value was lowest, 333 γ / in the 20—29 age group and highest, 354 γ % in the 30—39 age group. This difference, however was not significant ($p > 0.05$)

(b) Pöytyä

A serum specimen sufficient for the TIBC test was obtained from 180 men of whom 164 were »healthy» and from 214 women, of whom 168 were »healthy» The results are given in Table 21 and Fig 11 The arithmetic mean of TIBC in »healthy» men was 341 γ (range 250—482 γ) and in »healthy» women 353 γ (range 220—481 γ) 40.3 per cent of men and 48.8 per cent of women had values above 350 γ %.

A comparison of the mean values of the different age groups (Table 22) reveals that the lowest mean value among men, 330 γ was found in the 30—39 age group and the highest, 355 γ in that of 40—49 a significant difference ($p < 0.05$) The lowest mean value among women, 327 γ was that of the 20—29 age group, and the highest, 379 γ % that of the 40—49 age group. This difference between the groups was significant ($p < 0.001$) as was also the difference between the 40—49 age group and the over 50 (mean value 346 γ %, $p < 0.01$) and between the 30—39 (mean value 354 γ %) and 40—49 ($p < 0.05$) age groups.

Table 19. Distribution of the TIBC values for men and women of Ilomantsi

TIBC γ %	Men				Women			
	"Healthy"		Total series		"Healthy		Total series	
	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent
250—299	14	9 10	15	7.80	17	11.00	23	11.30
300—349	81	52.60	105	54.00	69	44.90	91	44 60
350—399	49	31.80	60	31 40	55	35.70	72	35.30
400—449	10	6.50	13	6.80	11	7 10	16	7.80
450—499					2	1.30	2	1.00
Total	154	100.00	191	100.00	154	100.00	204	100.00

the mean values of Hb and TIBC did not differ.

A study of the effect of parity on the low mean values of Hb and SeFe revealed that the influence of multiparity becomes apparent among quadriparas and quintiparas. These groups showed the lowest Hb and SeFe mean values. The fact that these multiparas obviously suffered from iron deficiency was reaffirmed both by the low Hb and SeFe values and by the high TIBC values. On the basis of the present investigation it is impossible to say why the values of the mothers of six or more children were higher. Furthermore, significant differences were noticeable in Pöytyä between the parous and the nonparous groups in the mean values of Hb, SeFe and TIBC, which supports the assumption that multiparas are more liable to develop iron deficiencies.

The husbands of women suffering from obvious iron deficiency were not affected by iron deficiency [illegible] the same extent as were their [illegible]ves. This is evident from Table [illegible] which gives figures for the husbands of women with more or less than [illegible] g/100 ml or 60 [illegible]. The haemoglobin and serum iron mean values grouped [illegible] showed no significant [illegible]. It may be concluded that iron deficiency did not occur by family even th[illegible] parishes showed several families with both husband and wife suffering from iron deficiency.

[illegible] investigation [illegible] [illegible] [illegible] correlation between the Hb and SeFe values. Vahlquist [illegible] [illegible] reported [illegible] where [illegible] Moreover were unable [illegible] relation between the Hb [illegible] SeFe [illegible]

In the present investigation a significant correlation was found in some but not all groups. Vahlquist found that, when the results were classified into four categories according to the serum iron values, a correlation was present in both the low and the high values but not in the medium values. The results now obtained suggest the same pattern. In the groups in which the SeFe mean values were low, e.g. the women of Ilomantsi and the men and women of Pöytyä, the correlation was significant while the groups with mediocre values, e.g. the men of Ilomantsi, national servicemen and student nurses showed no correlation. The present series contained no group with high values.

Beutler and his co-workers (1958) found a distinct correlation between a low SeFe and increased iron binding capacity of the serum in cases of severe iron deficiency anaemia but a less frequent correlation in mild anaemias. A similar conclusion was reported by Zuza and Block (1961) although their series contained only 7 severe cases and one mild. In the present investigation the correlation was calculated not on the basis of Hb content but for all the examined men and women grouped separately in the two parishes. A significant correlation was found in both parishes for both men and women but not for national servicemen or student nurses. The result obtained suggest findings similar to those of the investigations quoted, in that a significant correlation was obtained for the Ilomantsi and Pöytyä groups in which the SeFe was lower and the TIBC higher than among national servicemen.

A comparison of the results with those of earlier studies in Finland reveals that for men the mean values, Ilomantsi 13.7

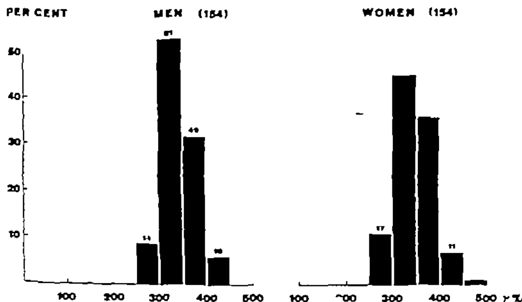


Fig 10 Distribution of the values of the total iron-binding capacity of the »healthy» men and women of Ilomantsi.

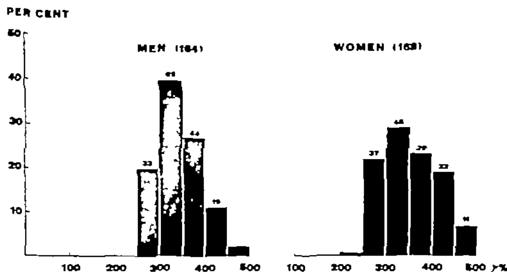


Fig 11 Distribution of the values of the total iron-binding capacity of the »healthy» men and women of Poytya.

are considerably closer to the mean values of the authors quoted than the relevant mean values for Ilomantsi and Pöytyä. The group of student nurses nevertheless included three with SeFe values below 60 γ [illegible] and the group of national servicemen included 15 whose SeFe values were below 60 γ. It is obvious that the investigation methods may have themselves contributed to the development of such differences but rather in that the previous investigations yielded values that were too high since only Powell of the foreign authors reported mean values of this high level.

A comparison of the present results with those achieved in the other Scandinavian countries reveals that only the mean value obtained in 1948 by Andersen and Norman, of Denmark, on a series of 293 men (14.2 g/100 ml), that obtained by R[illegible] of Denmark, in 1939 on a series of 19 men (14.1 g/100 ml) and that obtained by Nilsson, of Sweden, in 1948 on a series of 68 men (14.0 g/100 ml) concur with the present results. All Norwegian investigations have yielded higher [illegible] than [illegible] Danish and Swedish studies. [illegible] latest of the [illegible] that by Natvig of [illegible] covered 1 338 [illegible] The m[illegible] obtained was [illegible] Other foreign investi[illegible] the [illegible] 14.1 g/100 ml [illegible] by Pett[illegible] and Ogilvie [illegible] the mean [illegible] obtained [illegible] by H[illegible] on 37 men [illegible] the present results. All [illegible] reported considerably higher [illegible]

The SeFe me[illegible] reported in the Scandinavian countries and elsewhere differ quite distinctly from the present results. The lowest mean value was quoted for the series examined by Stengle and Schade of the United States in 1937, viz. 100 γ %. The mean values reported in other investigations range roughly from 110 to 130 % (Table 5).

The TIBC mean values for men quoted in international investigations vary considerably, ranging from 253 to 348 (Table 6). The series in these earlier investigations were relatively small, apart from those examined by Laurell (1947) and Rechenberger. Laurell quoted a mean value of 315 both for men and women and Rechenberger 309 γ for men and 30[illegible] for women. In his extensive survey of the literature Demulder reported a mean value of 300 γ [illegible] for both men and women, as the joint result produced by 8 writers.

A comparison of the mean values obtained in the present study (Ilomantsi 344 γ and Pöytyä 341 [illegible]) with the earlier investigations quoted shows that the present mean values are considerably higher. A study of the mean values by age group makes the contrast with earlier investigations seem even greater.

For women, too, the deviation from international studies follows the same pattern. Closest are the mean value 12.7 g/100 ml obtained by Andersen and Norman, of Denmark, on a series [illegible] 2018 women, the mean values obt[illegible] by Nilsson of Sweden on 56 [illegible] g/100 ml and by Lundström of Sweden, on 90 women in 12.0 g/100 ml and that by [illegible] of Norway on [illegible] 343 [illegible] g/100 ml. Other authors have

4 The effect of parity on blood values studied

A study of the effect of parity on the mean values of Hb, SeFe (morning values) and TIBC was made for »healthy» women of fertile age (20—49) whose last child had been born 1—5 years previously (Table 4) It was found that the lowest mean Hb value 11.2 g/100 ml, was for the group of quintiparas and the highest 13.2 g/100 ml, for the group of uniparas. The difference was significant ($p < 0.01$) Similarly the difference from the mean value for biparas 12.6 g/100 ml, was significant ($p < 0.05$) The difference between the mean values for quadriparas, 11.3 g/100 ml and for uniparas was also significant ($p < 0.001$) Compared with the biparas, triparas and sextiparas, the quadriparous group showed the same significant difference ($p < 0.01$)

The mean SeFe value was lowest, 35 γ % for quadriparas and highest for sextiparas, 79 γ % The difference was significant ($p < 0.001$) A significant difference was also shown by the quadriparas against the mean value of uniparas 62 γ % ($p < 0.001$) and against that of triparas 58 γ % ($p < 0.01$) The mean value for quintiparas, 42 γ % differed significantly ($p < 0.05$) only from that for sextiparas

The mean TIBC value was also highest for quadriparas, 390 γ % and lowest for sextiparas, 314 γ %. The mean value for quadriparas differed significantly from that of all groups other than the quintiparas, 373 γ % the significance against uniparas was $p < 0.01$ biparas $p < 0.05$ triparas $p < 0.05$ and sextiparas $p < 0.001$ The mean value for triparas, 350 γ also differed significantly ($p < 0.05$) from that for sextiparas.

The series has also been classified by the length of time from the last delivery into women whose last child had been born 1—2 years previously and those whose last child had been born 2 5 years previously The former series proved to be so small that, because of great dispersion, no significant differences emerged between the groups. The latter series complied with the results which the classification previously reported had also yielded

Table 24 Effect of parity Hb (g/100 ml) and SeF (γ %) content, Ferrometin and Pértyl combined

Parity	Number	Mean Hb and standard error	Number	Mean SeFe and standard error	Number	Mean TIBC and standard error
Uniparas	9	13.2±0.34	8	62±5.23	7	325±13.70
Biparas	18	12.6±0.23	17	48±7.06	16	349±15.01
Triparas	20	12 4±0.20	19	58±7 16	15	350±11.86
Quadriparas	11	11.3±0.34	11	35±3.53	11	390±14.88
Quintiparas	4	11.2±0.66	4	42±12.61	4	373±35.46
Sextiparas and over	16	12.6±0.28	15	79+10.67	15	314±10.08
Total	78	12.4±0.13	74	56±3.72	68	347±6.54

plenty of iron, and so had normal serum iron levels

The mean values of TIBC for women in the present series (Ilomantsi 343 γ and Puolanka 353 γ) were distinctly higher than those quoted in international papers (e.g. Laurell 315 and Rechenberger 307)

On the basis of the comparisons made it may be concluded that haemoglobin values and serum iron levels in the Finnish rural population are lower than those of other countries, with a possible exception of the Swedish rural population. It should be noted however that Waldenström's Swedish series dates back to 1946 when the years of war with their food shortages may still have affected the results. On the other hand the TIBC values of the Finnish rural population are definitely higher than in the other countries, particularly if it is borne in mind that 38.3 per cent of the healthy women of Ilomantsi and 40.3 per cent of those in Puolanka showed values exceeding 350 the figures for women were 14.2 per cent in Ilomantsi and 18.8 per cent in Puolanka. This fact suggests that a part of the Finnish population suffers from an iron deficiency which manifests itself in a low haemoglobin and serum iron content of the blood and in a high iron-binding capacity of the serum

It is known that iron deficiency may occur in the organism for the following reasons: haemorrhages, infections, tumours or an insufficient supply of iron in the food. Women may be affected furthermore by abnormally heavy menstrual discharge, frequent parturitions and lactation

In the series examined an attempt was made on the basis of medical history data, to take into account all the factors listed with the exception of an insufficiency of iron in food, and by this means a group termed »healthy» was formed from the total series

Since every effort was thus made to eliminate all pathological factors the only remaining possibility was an insufficient supply of iron. Is this true? Does the Finnish population not gain enough iron from its food

Turpeinen stated the opinion that the amount of iron contained in the staple Finnish diet was sufficient and even 2—2.5 times greater than required. He however estimated the average absorption percentage of iron at ?

Earlier investigations into the absorption of iron have mostly been indirect: the iron in food was ionized with hydrochloric acid and this ionized quantity was measured since only ionizing iron was believed capable of absorption in the digestive tract. These studies disregarded the effect of enzymatic digestion on the liberation of iron from foods. For this reason the only reliable basis that can be used in estimating the absorption of iron from foods is that provided by radioactive studies. Radioactive iron (Fe^{59}) was used by Moore and Dubach (1951) who found that the amount absorbed from food by normal subjects is at the most 10 per cent, and often less. Furthermore they found that the amount absorbed from spinach, lettuce and vegetables was under 10 per cent, a similar percentage was absorbed from egg and chicken liver while 30 per cent was absorbed from chicken meat. Similar results were attained by

Table 96. Correlations between haemoglobin and serum iron, and between serum iron and total iron-binding capacity

Hb–SeFe

Sex	Homanti				Polytya				National servicemen		Student nurses	
	Morning values		Evening values		Morning values		Evening values					
	Number	Correlation coefficient	Number	Correlation coefficient	Number	Correlation coefficient	Number	Correlation coefficient	Number	Correlation coefficient	Number	Correlation coefficient
Men	34	0.17 0.53	123	0.05 ± 0.09	86							
Women	138	0.18 ± 0.08	38	0.08 – 0.17	93	0.36						

SeFe–TIBC

Sex	Homanti				Polytya				National servicemen		Student nurses	
	Morning values		Evening values		Morning values		Evening values					
	Number	Correlation coefficient	Number	Correlation coefficient	Number	Correlation coefficient	Number	Correlation coefficient	Number	Correlation coefficient	Number	Correlation coefficient
				−0.03 ± 0.07	81	−0.60 ± 0.09	83	−0.6 ± 0.08				
	121	−0.66 ± 0.07	30	−0.85 ± 0.1	91	−0.60 ± 0.08	77	–				

considerable part of the cereal used in West Finland is wheat, the amount of iron obtainable from cereal products is still further reduced.

A large number of the men in Ilomantsi were forest workers whose daily diet according to an investigation by Karvonen et al (1961) contains considerably more iron (27 mg) than that of the rest of the population (13 mg) in the parish. The percentage of meat contained in their total calorie intake for instance was more than twice that of the rest of the population. Nevertheless, their haemoglobin value (13.5 g/100 ml) and serum iron level (58 [illegible] (evening value)) were below the lowest levels accepted for clinical use.

The present study provides no explanation for these low values but according to the investigation by Karvonen et al. the forest workers obtained this remarkably high quantity of iron mainly from cereal products, potatoes and meat. The amount of readily absorbable iron of [illegible] has consequently remained [illegible] smaller. It may also be assumed th[illegible] these men, engaged in heavy m[illegible] work, perspire much more than those working in other occupations and, [illegible] frequent the Finnish sauna wher[illegible] perspiration [illegible] they must lose [illegible] quantities [illegible] iron [illegible]

[illegible] West Finland [illegible] more bread, milk, butter and fish, West Finland more vegetables, fruit, margarine and eggs.

It is therefore quite obvious that the Finnish national diet contains too much dairy and cereal products. In order to ensure the necessary quantity of iron for the population, the proportion of meat, fish and eggs in the everyday diet should be increased. This conclusion was also reached by Järvinen et al. (1960) who studied the haemoglobin values of Helsinki children and found that children fed on »plenty» of milk and milk alone are fat but »on the other hand anaemic». According to Wasz-Höckert and Eklund (1962) the low haemoglobin values of girls, age 11—20 years, attending secondary school in Helsinki are similarly due to a deficient diet. The authors found that 24.2 per cent of the girls had haemoglobin values lower than 12.5 g/100 ml which is of the same magnitude as the values of the present investigation, i.e. 21.2 per cent for Ilomantsi women and 31.3 per cent for Pöytyä women.

This point is very well illustrated also by investigations carried out in Israel in 1950, 1952—53 and 1959—60 (Strauss et al. 1951, 1962). The mean value obtained in the former study for men was 14.2 g/100 ml and in the latter 14.7 g/100 ml, for women 12.4 g/100 ml and 12.9 g/100 ml respectively. The authors conclude that this rise in haemoglobin is correlated with a change in diet: the use of animal proteins increased by 16 per cent from the first to the second investigation.

It may justly be claimed that the [illegible] individuals of the present series [illegible] some whose iron deficiency is due

Table 20 Mean TIBC values and standard deviation i first and sec

Groups	Iron group						
	First examination			Second examination			Fir
	Number	Mean value	Standard deviation	Number	Mean value	Standard deviation	Number
Homa tal							
— Men	35	317	33.90	35	333	31.00	66
— Women	56	339	38.24	56	328	32.15	[illegible]
— Men + women	91	31[illegible]	36.61	91	330	31.81	[illegible]
Pöytyä							
— Men	82	349	49.55	82	320	39.08	[illegible]
— Women	62	358	62.91	62	390	54.68	92
— Men + women	144	355	55.66	144	332	46.45	358
Men							
— Homantal + Pöytyä	117	318	32.44	117	330	30.77	15
Women							
— Homantal + Pöytyä	118	319	33.28	118	332	13.[illegible]0	1 1
Total	235	319	19.37	235	331	11.33	96
National servicemen	20	325	30.00	20	335	20.51	
Student nurses	21	324	27.27	20	320	29.11	21

peratures do not affect these values. According to Pekkarinen the differences in the iron available from food are so small in the different seasons that this could not be of importance either.

The significant difference between the changes in mean [illegible] in the student nurse groups [illegible] decisively governed by the [illegible] the number of iron tablets [illegible] was twice that [illegible] Ilomantsi and P[illegible] also by the [illegible] according [illegible] the present [illegible] of tablets. The [illegible] among whom [illegible] the mean value changes of the groups were not significant even though the dose of tablets consumed was the same as that of the student nurses, were unable to convince the writer that they really had consumed the number of tablets they claimed to have had.

If the amount of iron in Ilomantsi and Pöytyä had been identical with that given to the national servicemen and the student nurses, the differences between the iron and placebo groups might perhaps have emerged more clearly for the blood values of those suffering from severe iron deficiency who had consumed iron tablets only would then have shown a more marked rise.

mean value 80 γ than those in P tyä, 39 γ

Compared on the basis of marital stat the unmarried men of Ilomantsi h d mean Hb value of 13 6 g/100 ml s ficantly lower ($p < 0.05$) than the n for the single men of Pöytyä 14 1 g ml. No such difference was discernibl SeFe mean values.

The mean Hb value for the natio servicemen, 14.2 g/100 ml did not d significantly ($p > 0.05$) from the m values for men of the same age (20 – years) in Ilomantsi (13.9 g 100 ml m Pöytyä (14.2 g/100 ml) The s m is true of the mean SeFe and TIB values.

On the basis of the investigation t n be concluded that the men of Ilomants and Pöytyä differed little from each other and even in cases where a significant difference could be noted, its sign ficance was within 5 per cent. This is also true of the national servicemen, domiciled in the province of Uusimaa when compared with men of the same age from the parishes of Ilomantsi and Pöytyä.

For women, the mean Hb value of Ilomantsi, 12.6 g/100 ml, compared with 12.4 g/100 ml in Pöytyä. The difference between these mean values was not sign ficant ($p > 0.05$) A significant difference did, on the other hand obtain between Ilomantsi and Pöytyä in the mean values of SeFe but not in those of TIBC (in Ilomantsi SeFe 68 γ , TIBC 345 in Pöytyä SeFe 45 γ and TIBC 355 γ)

By age group, too, the SeFe mean values in Ilomantsi were significantly higher than in Pöytyä. For the 20–29 age group Ilomantsi showed 77 γ and Pöytyä 52 γ ($p < 0.01$) for the 30–

1 g 100 ml n yä for t group

bl age group (20 – 29) m) D differences were not significant (p 0.05 but the SeF mean value fo student nurses, 93 was significa tly highe than that for the corresponding age gr p in Ilomants 77 γ ($p < 0.01$) nd in Pöytyä 52 ($p < 0.001$) Mea alues of TIBC howed no significant differences ($p > 0.05$)

Among the omen, t was fou d that the SeF mean values for Ilomantsi women were significantly higher than those for Pöytyä women. W th the mean values of Hb and TIBC, such differences were on ly noticeable for the 40 – 49 age group The SeF mean value for student nurses was also significantly higher than that for the women of comparabl age in Ilomantsi and Pöytyä, but in this age group

than the younger. Similarly, for women of 20–29 years the SeFe mean value in Pöytyä only was significantly lower than that for the older women. This age disparity is not similarly visible in TIBC mean values.

By type of occupation, it was found that the Hb mean value for men engaged in intellectual work was in both parishes significantly higher than that for men in heavy manual work. For women the same is true of Pöytyä but in Ilomantsi no significant difference existed. Since the SeFe mean values were distributed into morning and evening values by the hour of taking specimens, the morning value groups, which were involved in the comparison, remained so small that due to dispersion, no significant differences were noted between those engaged in heavy manual work and in intellectual work, even though the mean values of the intellectual workers are generally higher. TIBC mean values were not treated at all on the basis of the type of occupation.

No significant differences were noted in the mean values of Hb, SeFe and TIBC for married and single men. The unmarried women of Ilomantsi were found to have significantly higher Hb mean value than the married women, but not so those of Pöytyä, where the significance of the results was evidently affected by the small series and great dispersion. Nor did the SeFe and TIBC mean values show any significant difference.

For the influence of parity on the mean values of Hb, SeFe and TIBC it was found that the lowest Hb mean value was shown by the group of quintiparas and the lowest SeFe mean value by the group of quadriparas, in which the TIBC mean value was also highest. The differences, apart from the Hb mean values of Ilomantsi, were significant, with a few exceptions.

A comparison of the Hb and SeFe values of the husbands, or other family members attending the examination, of the women whose Hb value was below or above 12.0 g/100 ml or serum iron level below or above 60 γ revealed no significant differences between the mean values of groups so made up. Iron deficiency was not therefore found to occur by family even if there were numerous families in which both husband and wife suffered from iron deficiency.

A positive significant correlation was noted between haemoglobin and the morning values of serum iron in Ilomantsi women and Pöytyä men and women, but not in Ilomantsi men, national servicemen or student nurses.

A positive significant correlation between the serum iron level and total iron binding capacity of the serum was found to exist in Ilomantsi and Pöytyä among both men and women, but not among the national servicemen or student nurses.

The quantity of iron tablets consumed from one examination to the next was not found to have increased the Hb value or SeFe level of those who had had iron tablets, whereas the TIBC values were found to have declined in both parishes. For student nurses, the increase in Hb and SeFe values was found to be significant, while this was not so for the national servicemen. The slight effect of iron therapy was attributed mainly to the fact that members of one and the same family had received both iron and placebo tablets and consequently members of the placebo

g/100 ml Pöytyä 13.9 g/100 ml and national servicemen 14.2 g/100 ml, corresponded most closely to the mean value 13 8 g/100 ml obtained by Turpeinen and the mean value 13 f g/100 ml of the »1915 – 1946 material» The mean value obtained by Tötterman and P tulä, 13.3 g/100 ml and that reported by Setälä, 13 4 g/100 ml are dist nctly lower

The situation is reversed for the SeFe mean values previously found n Finland Primarily worth noting are those reported by Hirvonen 140 γ by Totterman, 141 and by Fredrikson, 145 γ The mean values of the present study Ilomantsi 72 ‰ Pöytyä 66 ‰ and national servicemen 98 were distinctly lower TIBC studies have not previously been carried out in Finland and no comparisons are therefore possible.

For women the mea Hb value closest to those of the present study Iloma tsi 12.6 g/100 ml Pöytyä 12.4 g/100 ml and student nurses 12.9 g/100 ml, was that obtained by Patulä, 12.2 g/100 ml while other authors (the »1915 – 1946 material» Tötterman, Setäla and Turpeinen) reported a mean value of 12.1 g/100 ml and Harjola 12.0 g/100 ml. For SeFe mean values the situation among women was the same as that for men The mean values reported by earlier authors, H r vonen 119 γ ‰ Harjola 95 γ Tötterman 122 γ ‰ and Fredrikson 124 γ ‰ were higher than those obtained in the present study Iloma tsi 68 γ Poytyä 45 γ % nd tudent nurses 93 γ %

A comparison of mean values by ge group has only previously been under taken in Finland by Setälä, whose age classification was in 5-year groups. The mean Hb values for men aged over 55 years were found to be lower than those for the younger men In the present series the mean value for men aged 30 – 39 (14 0 g/100 ml in both parishes) was higher than that for men over 50 years of age. The difference in Ilomantsi was sig nificant ($p < 0.01$) Of these earlier in vestigations, only that by Setälä is truly comparabl w th th present study His series was considerable in size and could not be described as selected, as were the other investigations.

The mean haemoglobin values of the earlier investigations come closer to those obtained for the present study when it is realised that King and Gilchrist (1947) f und that the Haldane standard employed th earlier investigations had given values which were 4 – 5 per cent too low If for example, the mean value fo women reported by most uthors, 12.1 g/100 ml is increased by 5 per cent, the mean value will be 12.7 g/100 ml, which is in precisely the same class as the present results.

The present SeFe mean values are low compared with th earlier investigations mentioned but t must be pointed out that all the earlier investigations were based on f lly selected series comprising healthy individuals who were, in addition, mostly young town dwellers. These investigations do not, for instance, include any low values (under 80 or 60 γ %) for men or for women. In the present study not even the groups of national servicemen or student nurses were similarly selected although in the present series they represent selected groups. As a result, the mean value of 98 γ % for the national servicemen and 93 γ % for student nurses

REFERENCES

A ARWAL, S. G. and MITRA, S. S. Observa ions on the level of unsaturated iron-binding capac ity total iron-binding capacity and saturation percentage in pathological subjects. Indian J med.Res. 43:403 1955

ALAMERA, R. and PÖYTTÖNE P Johdatusta ilastolliseen tutkimukseen. Helsingin Yliopisto, Hel sinki, 1954

A DERSE A. H. and NORMA H Hemoglobin values in families of Danish working lass during 1940—42. Nord.Med. 37 108 1948

ANDERSSON, N. S. E.: Experimental and clinical investigations into the effect of parenterally administered iron. Acta med. scand. 138, suppl. 241 1 1950

APPELBE G, R. Om karcinomanemien natur Tryckeri — & Tidningsaktiebolagets try keri, Porvoo 1919

B KAN G and WALKER, B.: Determination of serum iron and pseudohemoglobin iron with o-phenanthroline J.biol.Chem. 135:37:1940

BECK R, C Om blodbilden hos hemocephalus-barn Finska Läk. Sällsk.Handl. 57 1 1915

BE Y W T C., COWLY P J and MASSE, H. E.: Haemoglobin levels in adults and hildren. Brit.med.J 1-410-195

BE TLER, L., ROBSON, M. J and B TTENWIESER F A comparison of the plasma iron, iron-binding apacity sternal marrow iron and other methods in the linical evaluation of iron stores. Ann.Int. Med 49 60 19 8

BIE NO, F and NON NIX, G. Haemoglobin-bestemmelser med an Slyke tandardiserede haemometre erythrocyttaellinger og cellevolumenbestemmelser paa normale. Ugeskr.Laeg 99 827 193

BIRTHÖW C O On the morphology f blood and bone-marrow in th protozoan. Acta hiurg Scand 94 suppl 114 1 194

Bj as and Grunewald N Serum iron determina in in diagnosis f acute hepat is nd her forms of jaundice Nord.Med. 3314 19

Be er J I I er I ersuchung uber die Farbe kraf des I es und die Anzahl roter Blutkor perchen bei waschen auf 70 n Be Acta med.scand v 1 5

BRAUNSTEINER H., GISINGER, F and P KISCH, F Ferritin, Transferrin und Serumeisen. Klin. Wschr 30:394 1952

BRE DAHL P: Serum iron, total iron-binding capacity of serum and serum copper in normals. Scand.J.clin.Lab.Invest. 5:312:1953

BROCHNER MORTENSE K. Om serumjern. Bibl. Læger 135:501:1943

BROCHNER-MORTENSE K. and OLSE C. Colorimetric method for determina ion of iron in serum with investigation of iron content of nor mal human serum. C.R.Lab., Carlsberg 23 235:1940

CALLENDER, S. T M LLER B. J and S ITH, M. D Absorption of haemoglobin iron. Brit. J Haemat. 3 186:1957

CANN N, R K. Proposal for certified standard for use in hemoglobinometry — second and final report J Lab.clin.Med. 52:471:1958

CARTWRIGHT G E., HUGULEY C. M. Jun., ASCHENBRUCKER, H., F Y J and WINTROBE M.M. Studies on free erythrocyte protoporphyrin, plasma iron and plasma copper in normal and anemic subjects. Blood 3 501:1948

CARTW IGHT G. E. and WINTROBE, M. M.: Chemical, clinical and immunological tudies on the products of human plasma fractionation. XXXIX. The anemia of infection. Studies on the iron-binding capacity of serum. J clin. Invest. 28 86 1949

CHALO KA, M., LEVI ON R. M and DIEN ERGER F: Serum iron and hemoglobin values of 275 healthy women. Proc Soc.exp.Biol. 77: 677 1951

CHODOS, R. B., ROSS, J F APT L., POLLYCOVE M. and HALKETT J A. E.: The bsorption of radioiron labeled foods and iron salts in normal and irondeficient subjects and in idiopathic hemochromatosis. J clin Inves 36 314 1957

CROSBY W H M NN, J I and F RTH, F W Standardizing method f clinical hemoglobinometry U S armed Forces med. J 5 693 195

DAHL, S.: Serum iron in normal women. Brit med J 1 731 1948

D VIES, C LE B. and OHL SOLLE N, N G. The microestimation of serum iron and iron-

figures ranging from 15 0 to 14 0 g/100 ml. Among investigations published elsewhere in Europe and in the United States, results of the same magnitude were reported in 1958 by Judy and Price U.S.A. on 663 women, 12.6 g/100 ml, Pett & Ogilvie Canada on 329 women 12.6 g/100 ml and earlier in the U.S.A. by Milam and Muench (1946) on 838 women, 12.9 g/100 ml.

For SeFe mean values the differences are not quite so great compared with relevant international investigations, for the lowest of the mean values reported in earlier investigations (and quoted in Table 5) was 84 γ obtained by Eckeström in 1944 on Swedish geriatric subjects, and 89 γ obtained by Heilmeyer and Plötner on German women. The highest was the mean value 127 γ % obtained by Brochner-Mortensen and Olsen in 1940 for Danish women, and by Lundström for Swedish women. The mean value for the student nurses in the present series remained within the limits quoted, even though it belonged to the lowest class.

It is of interest to compare the results obtained in the present study with those quoted by Waldenström in 1946 on a series of women of the province of Upsala, in a typical rural parish (B) of nurses deriving from these parishes but working in Upsala, of fishermen's wives (M) and two series of women living in urban districts (S and U). Their mean SeFe values were

Rural population B (142) 7? ± 2.5 γ %
» » M (101) 80 ± 3 5 γ %
Nurses of population
B (28) 96 ± 5 8 γ %
Urban population S (26) 101 ± 7.5 γ
» » U (54) 91 ± 3 7 γ %

22 per cent of the rural population of the parish of B showed an SeFe value below 4 and 29 per cent below 55 γ while only 7 per cent of the nurses coming from the same province had SeFe values below 55 γ. Among the rural population M 15.8 per cent had SeFe values below 40 γ. In the urban population S only one woman had a low SeFe value and in population U only four (7 4 per cent) had a low value.

In the present series, the mean value of Pöytyä women, 58 γ was distinctly lower than that of Waldenström's rural population, while the mean value for Ilomantsi, 68 γ %, is on the same level as was rural population B in Waldenström's material. In this same population, Waldenström found values below 55 γ % in 29 per cent, while in the present series 42 5 per cent of Ilomantsi women and 73 7 per cent of Pöytyä women showed values under 60 γ %. The mean value of the student nurses, 93 γ %, however very nearly equals the mean value Waldenström quotes for his series of nurses, 96 γ the difference in Waldenström's study and the present investigation between nurses (student nurses) and rural population is of the same magnitude.

Waldenström interprets these low serum iron levels as the result of a low iron content in the diet of the rural population. He supports this contention by observing that the nurses who originated from this same population had for a minimum of three years at the hospital had a diet of animal proteins (meat) containing

Chodos and his co-workers (1937), b t the quantities absorbed were still les 0.5—5 per cent. Callender et l 10 found that some 11 per cent of tl in haemoglobin was absorbed. St with bread cereals have shown th absorption of radioactive iron a l flour before baking was, acc Sharpe et al. (1950) 4 4 per c according to Pirzio-Biroli et al per cent. Moore and Dubach l that it was very difficult to complete study of iron absorp a normal dietary regime, but a of 5—10 per cent is a fa assessment of an average p absorption

If this percentage of bsorp basis of Turpeinen s study starting point the suff available n the Finnish diet into question even accordi g t l

A clearer picture of the suff iron a ailable however is p l l l the dietary study carried u l Pekka rinen in connection w th the ep d mio- logical field study of the Fin h H rt Association in 1956 1957 nd 1 5 This n tritional study was part carried out in the same parishes, Ilomantsi and Pöytya, as those of the present estig tion. The investigation was ery thorough, and the foodstuffs consumed by 4 + 20 + 30 families in East Finland and 41 + 20 + 30 families in West Finland were carefully weighed. The a thor found that in both East and West Finland the 24-hour diet included 12—14 mg of iron (mean value of the studies effected) The absorbed amount, according to Moore (1955) would then be 0.6—1 4 mg per day When a man loses an average of 1 5 mg and a woman of fertile age her 0.5—1 0 mg on an average of per day the conclusion must be that the iron content of the diet is l not sufficient for everybody A t n of the men and the majority of men of fertile age fail to obtain iron and suffer from a continuous eficiency According to Moore and h a quantity of 12—15 mg of iron hould suffice but evidently the t to meet the daily requirement is) tainable from the said 12—14 mg u ed in the staple Finnish diet.

t does this deficient diet consist of? l gh the indi iduals examined in the t series were asked about the t ties of food they consumed, it is rferable to refer to Pekkarinen s investi- z tion since th results there quoted are nsiderably more accurate. This investi g tion reveals that the most important ces of energy in these parishes were cereal products (30 per cent) butter (9—13 per cent) nd other dairy products 20 25 per cent) meat (5—8 per cent) potatoes (5—7 per cent) sugar (9—11 per cent) margarine (3—6 per cent) eggs 0.6—1.8 per cent) and fish (1—2 per cent) The most important sources of energy are known to be meat, fish and eggs, and cereal products ground from whole grain. Pekkarinen s results also reveal that the quantity of the most important iron-containing foodstuffs, apart from cereal products, was only slightly more than 10 per cent, and that the most important source of iron in the Finnish diet is cereal products. From these is btained approximately half the total iron quantity in East Finland even more. If, moreover it is borne in mind that a

not to dietary but to quite other factors. This is possible since sick people and expectant and lactating mothers were excluded on medical history data alone. The number of those suffering from iron deficiency for other reasons, however may be assumed to be negligible.

Ilomantsi is in that part of Finland where nearly a third (27 2 per cent) of the population are fish tapeworm (Diphyllobothrium latum) carriers (Nyberg et al. 1961). According to the same investigation 1.9 per cent of the tapeworm carriers have megaloblastic anaemia and 1 1 per cent suspected vitamin B deficiency anaemia. Accordingly the present series should include 1—2 men and women of Ilomantsi with megaloblastic anaemia. In megaloblastic anaemia the haemoglobin is low serum iron high and iron binding capacity small. These few sources of potential error are so small that they do not affect the mean values of population groups obtained in the investigation.

It was reported in the chapter on results that iron therapy administered to one half of those examined did not appreciably increase the Hb and SeFe values in Ilomantsi and Pöytya, judged by a comparison of the differences between the changes in mean values the difference between the mean value changes for the iron and placebo categories was not significant in any group. The effect of iron on the examined was smaller than assumed as is also seen in the standard deviation of the mean values which in many cases had not changed in the interval. It may be assumed however that iron therapy had its effect on those examined but that certain factors which will be discussed later rendered the changes insignificant.

Iron therapy may be considered to have had a definite effect on the group of student nurses, for in this group a significant difference in the changes in Hb and SeFe mean values between the iron and placebo groups was obtained. In the other groups the TIBC values can be taken to have dropped as a result of iron therapy. The TIBC values of those suffering from iron deficiency fall during iron therapy while iron stores gradually begin to build up, and they only become normalized after the building up is complete (Konttinen 1955). Some of the iron groups examined showed a definite improvement of iron stores, e.g. the SeFe mean value of Pöytya women rose significantly from 4[illegible] % to 63 γ. Since the mean value of the placebo group however also rose simultaneously the difference between the changes was not significant. Why did this happen? The most probable explanation is that since iron and placebo tablets were distributed to the examinees so that one had iron and the next placebo, irrespective of whether or not the examinees were members of the same family at least half the number of families had both iron and placebo tablets, the husband having the one and the wife the other. Since the packings were identical the probability is very great that within the same family the two packs were confused and especially that tablets were eaten from one and the same pack, with the result that members of the placebo group also had iron.

It is hardly probable that a factor like the change of season from the first to the following examination could have affected the increase in the mean values of both groups, since it has been indisputably found that seasons of the year and tem-

CONCLUSIONS

The results of the investigation suggest very strongly that at least a part of the Finnish population suffers from continuous iron deficiency. This deficiency has been found to be commoner among women in the West Finnish parish of Pöytyä than in the East Finnish parish of Ilomantsi, while no difference was noted between the men of the two parishes. Among the national servicemen from different parishes of South Finland, iron deficiency is of the same magnitude as that of the young men of the same age groups in Ilomantsi and Pöytyä. On the other hand, the iron deficiency among student nurses coming mainly from towns is definitely lower than that of the young women of the same age in Ilomantsi and Pöytyä.

This iron deficiency is reflected in all the groups in the form of low haemoglobin values and serum iron levels and a high iron-binding capacity of the serum. Although in the present study the addition of iron to the diet was for various reasons a partial failure, this deficiency can evidently be rectified by iron therapy. It is obvious, however, that for the national health the only correct way of remedying iron deficiency is to seek to change the dietary regime. Efforts should be made to increase the proportion of animal proteins, rich in iron, and to reduce that of dairy products, poor in iron, in the national diet.

group had also had iron tablets, so that the increase in mean values from one examination to the next became significant in this group, too

The results were compared with earlier investigations published at home and abroad and the differences between them and the factors governing these differences, especially the dietary regime, were discussed The conclusion reached on this basis was that the Finnish national diet does not contain enough absorbable iron and that a part of the population suffers from iron deficiency